DISEASES OF THE CHEST

VOLUME 1

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DISEASES OF THE CHEST

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PREFACE

THIS book on Diseases of the Chest by thirty-one authors has in
considerable organization, and our thanks are due to the patience and
humour of the authors of the various sections. An attempt has been m
render the volumes reasonably comprehensive, and to avoid undue overla
Advances, especially in the field of Chemotherapy, are developing rapidly.
able as they are, they may be regarded as powerful accessories to, rather t
substitutes for, established scientific techniques, and we hope that th
little in this book which will have to be discarded after standing the test o

A chapter on Physiotherapy has been included, a small acknowledgm
the importance of this subject to those who are responsible for the trea
of patients suffering from diseases of the chest

Our thanks are due to Drs M H Jupe, R S. Murray, E. G Sita-Lu
and L. B Stott for supplying us with x-ray photographs for reprodu
to Dr D Barron Cruickshank, Mr. J. P. Entract, and Mr T Cawl
assistance in checking the Bibliography, and to Drs I C. Lodge
H C. Hamilton and C Bartley for help in reading the proofs

GEOFFREY MA
KENNETH PERR

June, 1952

CHAPTER 1

BRONCHO-PULMONARY ANATOMY

A. F. FOSTER-CARTER

IN THE past twenty years the detailed anatomy of the bronchial tree and lungs has acquired great practical importance and much has been written on the subject. Nevertheless, in spite of recent advances, we must still acknowledge and admire the work of William Ewart who published his monograph on the bronchi and pulmonary blood vessels in 1889. Ewart may fairly be called the father of bronchial anatomy, with great ingenuity he succeeded in making casts of the pulmonary vessels in Wood's metal and his anatomical description was so accurate that much of it has remained unchanged to this day. He was also the first to describe the broncho-pulmonary segment, which has since become the key to our understanding of pulmonary anatomy. Ewart wrote of separate "territories of ventilation" within the pulmonary lobes, each supplied by a bronchial branch and having no communication with its neighbours. The existence of these territories, which we now call broncho-pulmonary segments, has been amply confirmed by recent anatomical and embryological studies.

[illegible] ... [illegible] ... [illegible] ... [illegible] somewhat resembles that of a blackberry [illegible] each of which is a developing bronchial bud. [illegible] jostle one another during development, and [illegible] expense of their neighbours. For [illegible] which are the finished products of the bronchial [illegible] relative sizes in different lungs.

A broncho-pulmonary segment is a wedge of lung tissue [illegible] bronchus and, just as the pulmonary lobes are [illegible] areas of lung supplied by different bronchi within a lobe are [illegible] down to the terminal lobules. For practical purposes [illegible] between adjacent broncho-pulmonary [illegible]. When [illegible] is injected into a given bronchus the segment of lung [illegible] bronchus is distended with the injection [illegible] ing segments. In fact, the broncho-pulmonary [illegible] partitions which can be traced [illegible] are not obvious. When a broncho-pulmonary segment [illegible] septa often become thickened and [illegible] naked eye (Fig. 1). Also it is not unusual to [illegible] individual broncho-pulmonary segments.

It will be seen that the lung can be divided into [illegible] segments, depending upon the size of the [illegible]

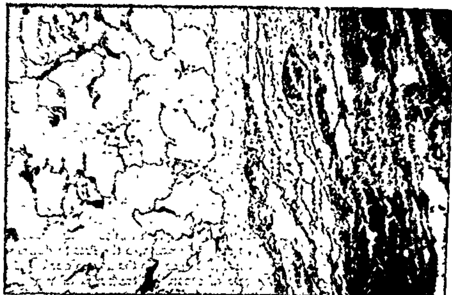


Fig 1 —Inter-segmental boundary The thickened and oedematous inter-segmental septum can be seen in the centre, with a normal segment on the left and a collapsed segment on the right

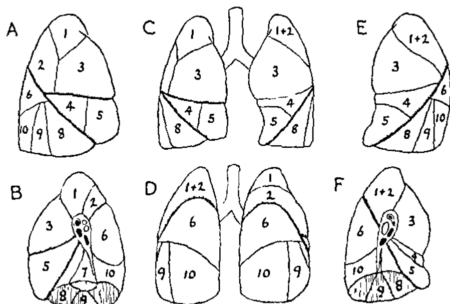


Fig 2 —Diagram of the broncho-pulmonary segments
A Right lung, lateral view
B Right lung, medial view
C Both lungs, anterior view
D Both lungs, posterior view
E Left lung, lateral view
F Left lung, medial view
(For key to numbering *see* Table)

An arbitrary choice must be made and it is convenient to define a broncho- [illegible]

[illegible] equivalent to the upper and middle lobe bronchi of the right lung) If these branches are chosen as segmental bronchi, the lungs will be divided into a reasonable number of large segments which vary very little in their distribution (Fig 2), whereas if smaller branches are described, the whole picture becomes very complicated and the smaller units do vary considerably in their relative sizes More important still, pathological processes usually involve the large segments and they can often be recognized radiologically

Figs 2 and 3 show the common arrangement of the human bronchial tree and the broncho-pulmonary segments ; they are based on studies of injected specimens, dissections and casts and the nomenclature and numbering is that recommended by the Thoracic Society of Great Britain (1950) in consultation with an International Committee (*see* Table).

TABLE

NOMENCLATURE OF BRONCHIAL TREE AND BRONCHO-PULMONARY SEGMENTS

Right upper lobe bronchus	*Left upper lobe bronchus*
Anterior (3)	*Upper division*
	Anterior (3)
	Apico-posterior (1 and 2)
Apical (1)	Apical (1)
Posterior (2)	Posterior (2)
Right middle lobe bronchus	*Lingula* (lower division)
Lateral (4)	Superior (4)
Medial (5)	Inferior (5)
Right lower lobe bronchus	*Left lower lobe bronchus*
Apical (6)	Apical (6)
Medial basal (cardiac) (7)	
Anterior basal (8)	Anterior basal (8)
Lateral basal (9)	Lateral basal (9)
Posterior basal (10)	Posterior basal (10)

Fig 4 shows a series of bronchograms corresponding to the diagrams of the bronchial tree [illegible]
left posterior) ol [illegible]
45° to the film [illegible]

NORMAL BRONCHIAL ANATOMY

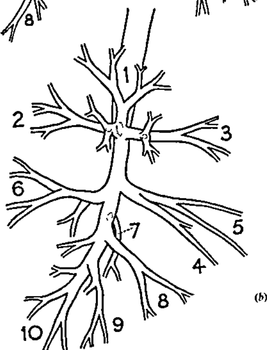
(The numerals appearing after some headings refer to the bronchi and segments shown in Figs 2 and 3)

Right upper lobe

[illegible]

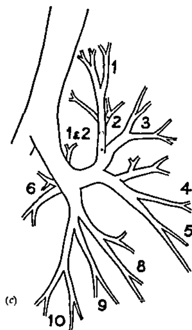
[illegible] aspect of the upper part of the right main bronchus and after a short course of about 1 centimetre it divides into three branches

(a)

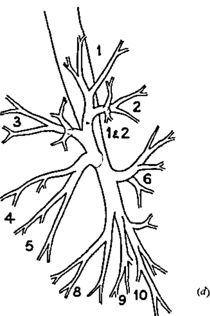


(b)

FIG 3—Diagrams of the normal bronchial tree (*a*) Anterior view, (*b*) Right lateral view, (*c*) Right anterior oblique view, (*d*) Left lateral view (For key to numbering *see* Table on page 3)



(*c*)



(*d*)



(*a*)



Fig 4.—Normal bronchograms (*a*) postero-anterior, (*b*) right lateral, (*c*) right anterior oblique These bronchograms should be compared with the corresponding diagrams in Fig 3 to identify the individual branches (*By kind permission of Dr G Simon*)

(*b*)



FIG 4 (c)

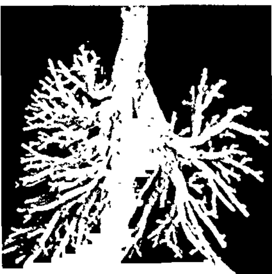


FIG 5—Celloidin cast of the bronchial tree at birth Right anterior oblique view (for comparison with Fig 3 (c)) Note the long descending, paravertebral branch of the left lower apical bronchus (6) Also the upward displacement of the apical branch of the right upper lobe bronchus (1)

Apical (1).—This branch goes directly upwards and shortly divides into a prominent V which is easily recognized in bronchograms (Fig. 4*b*). Consolidation of the apical segment appears as a dense shadow filling the dome of the pleura and tapering downwards to the hilum.

Posterior (2).—This branch is directed backwards and slightly upwards to supply the postero-lateral part of the lobe. Soon after its origin it gives off an important lateral branch. The posterior segment is often picked out by aspiration infections and becomes the site of pneumonia or lung abscess. It is also the most common site of post-primary tuberculosis and has acquired additional importance now [illegible]
culos[illegible]
as a [illegible]
the periphery; the shadow becomes much less dense as the narrow part of the wedge approaches the hilum (Fig. 6*a*). In the lateral radiograph, the shadow is uniformly dense and situated posteriorly, extending forward to the mid-axilla (Fig. 6*b*). Lateral tomographs are often helpful in visualizing this segment.

Anterior (3).—This branch extends horizontally forwards and also provides an important lateral division soon after its origin. Consolidation of the anterior segment produces a dense shadow above the middle of the lung field in the postero-anterior radiograph (Fig. 7*a*). The lower border is sharply defined by the lesser fissure and the density extends right to the mediastinum which distinguishes it from a consolidation of the posterior segment. In the lateral view the shadow is situated anteriorly and extends back to the mid-axilla where its maximum density is situated (Fig. 7*b*).

Lateral or "axillary" area of the right upper lobe

There has been some confusion in the past concerning the bronchial supply to this area. Fig. 8 shows a cast of the right upper lobe bronchus of a human foetus viewed from above, which demonstrates clearly the most usual arrangement. It [illegible] the lateral branches of [illegible]

some earlier workers. Boyden and Scannell (1948) have shown that in 16 per cent of cases the lateral branch of the posterior bronchus arises directly or almost [illegible] The Thoracic [illegible]

Right middle lobe

The right middle lobe bronchus arises from the antero-lateral aspect of the right main bronchus and extends forwards, outwards and downwards. It divides into two principal branches.

Lateral (4).—This branch supplies a wedge extending from the hilum and reaching the posterior half or two-thirds of the lateral surface of the lobe.

FIG 6.—Consolidation of posterior segment of right upper lobe (*a*) Postero-anterior radiograph showing consolidation due to chronic suppuration, (*b*) Lateral bronchogram of same patient showing obstruction of the posterior bronchus in the consolidated segment, confirmed at autopsy (*By courtesy of Amer J Dis Chest*)

(*a*)

(*b*)



(a)



(b)

FIG 7—Consolidation of anterior segment of right upper lobe (a) Postero-anterior radiograph showing consolidation of the anterior segment due to a lung abscess (b) Lateral radiograph of same patient (*By courtesy of Amer J Dis Chest*)

Medial (5)—This bronchus supplies the remainder of the lobe, including the medial and anterior aspects and the anterior part of the lateral surface

Consolidation and collapse of these segments, either separately or together, is not an infrequent occurrence and is easily recognized in radiographs In the postero-anterior view the shadow extends out from the lower part of the hilum if the medial segment is involved but is more peripheral at the same level when the lateral segment is affected A lateral view is essential to distinguish middle lobe lesions from those in the apical segment of the lower lobe Consolidations of the individual middle lobe segments may be distinguished by their position in the lobe as shown in the lateral radiograph



FIG 8—Celloidin cast of the right upper lobe bronchi 20 weeks' foetus Viewed from above to show the large lateral branches of the anterior and posterior bronchi Scale in millimetres

Left upper lobe

It is common knowledge that the left upper lobe is equivalent to the right upper and middle lobes and it is convenient to consider its anatomy at this stage As one might expect, the left upper lobe bronchus has two main divisions corresponding to the bronchi of the upper and middle lobes in the right lung

Upper division

[illegible]

of the posterior segment may be involved separately in pathological proc[illegible] is more common for the apico-posterior segment on the left side to be a[illegible] whole. Consolidation of this segment appears in the postero-anterior [illegible] as a dense shadow filling the whole apex of the lung, with its lower bord[illegible]

upwards from the hilum In the lateral view it can be distinguished from consolidation of the anterior segment by its posterior position

Anterior (3) —The anterior bronchus of the left lung resembles that of the right but usually supplies a larger area which extends backwards to the inter-lobar

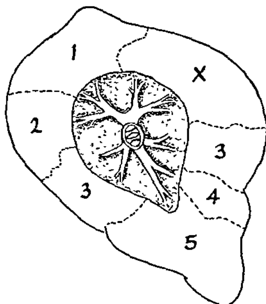


Fig 9 —Sketch of dissected and injected left upper lobe *(after Scannell, 1947)* Medial aspect, showing a trifurcate branching of the upper lobe bronchus caused by downward displacement of the anterior segmental branch (3), *which forms the central limb of the trifurcation* An accessory bronchus (X) supplies the area usually occupied by the anterior segment

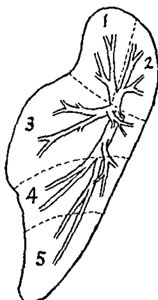


Fig 10 —Diagram of the bronchi and segments of the left upper lobe *(after Boyden, 1949)* Lateral view Note that the *lingula bronchus has three important* branches, superior, inferior, and lateral

fissure and thus compensates for the small size of the posterior segment The radiographic characteristics of consolidation of the left anterior segment are also *similar to those of consolidation of the right anterior segment*

Lingula (lower division)

This bronchus corresponds to the right middle lobe bronchus In most instances it is long and divides into two branches, superior and inferior Boyden (1946) has shown that in 22 per cent of cases it divides early into an upper and postero-laterally placed bronchus and a lower and antero-medially placed bronchus. This variation corresponds more closely to the lateral and medial *arrangement of the right middle lobe segments, but the superior, inferior* pattern is more usual in the lingula.

Superior (4) —This bronchus supplies the upper part of the lingula area and has a large lateral branch (Fig. 10), this sometimes arises separately higher up the [illegible] per cent) and accounts for some examples of the *segmental* [illegible] segment is

Inferior (5).—This branch supplies the lower part of the lingula area, including the anterior tip.

Consolidations of the individual lingula segments are difficult to identify in radiographs because they are superimposed on the heart shadow in the lateral view. However, lesions of the lingula as a whole are more common than those of its sub-divisions and consolidation of the lingula can be recognized in the postero- [illegible] sharply defined inferior margin where it is bounded by the inter-lobar fissure.

The work of Boyden (1949) has shown that many hitherto unsuspected variations occur within the prevailing pattern of the bronchial tree, particularly in the left upper lobe. Displacement of branches from one position to another is relatively common and accessory bronchi are found, which probably represent displaced branches from elsewhere. For instance, Boyden has shown that in the trifurcate arrangement of the branches of the left upper lobe bronchus (Fig. 9) which occurs in 26 per cent of cases, the branch which resembles the anterior segmental bronchus [illegible]

variations are important to the surgeon performing a segmental resection because they are associated with abnormal vascular patterns (Boyden, 1946), but for practical purposes they do not interfere very much with the radiographic and bronchographic interpretation of bronchial and segmental lesions.

The lower lobes

The broncho-pulmonary anatomy of the lower lobes is very similar in the two [illegible] Each lower lobe has an [illegible] there is a fourth basal [illegible]

Apical (6).—This is the first branch of the lower lobe bronchus. It is directed backwards and is of considerable importance because the lower apical segment is a common site of pulmonary tuberculosis and of non-specific infections. The [illegible] commonly has three sub-divisions, apical, supplying the actual apex of the lobe, [illegible]

(Fig. 11*a*). In the lateral view there is a characteristic posterior triangular opacity, bounded in front by the great fissure, behind by the chest wall and below by a less definite, horizontal lower border (Fig. 11*b*).



(a)

FIG 11 —Consolidation of apical segment of right lower lobe (a) Postero-anterior radiograph of consolidation of right lower apical segment due to pneumonia, (b) Lateral radiograph of same patient (*By courtesy of Amer. J. Dis Chest*)



(b)

Medial basal (cardiac) (7) —This is the next branch of the lower lobe stem in the right lung, it arises from the medial aspect, just below the origin of the apical branch, and is directed downwards to supply a small segment on the medial aspect of the lobe alongside the heart The medial basal bronchus usually describes a marked curve with its convexity forwards and this is a help in recognizing the [illegible]

since the diaphragmatic surface of the lower lobe is naturally divided between four basal segments of which this is one The medial basal bronchus is represented in the left lung by a branch of the anterior basal bronchus which supplies a similar area and has an identical blood supply , it differs only in its origin from the anterior basal and very rarely it arises separately from the lower lobe bronchus as in the right lung

Consolidation of the medial basal segment shows on the postero-anterior radiograph as a small shadow filling the right cardio-phrenic angle and extending up along the right border of the heart Laterally it appears as a small triangular opacity, based on the centre of the diaphragm and tapering up to the hilum

Anterior basal (8) —This important branch arises from the anterior aspect of the lower lobe bronchus and is directed downwards, forwards and laterally Consolidation of the anterior basal segment frequently occurs in the course of pulmonary infections and can easily be recognized Postero-anteriorly the shadow is most dense in the costo-phrenic angle region, whence it extends upwards to the hilum leaving the cardio-phrenic angle clear on the right side (Fig 12*a*) In the lateral film there is a dense, band-like shadow slanting downwards and forwards from the hilum to the diaphragm , it is bounded in front by the sharp line of the inter-lobar fissure and is often wrongly diagnosed as an inter-lobar effusion (Fig 12*b*)

Lateral basal (9) —This is one of the two terminal branches of the lower lobe stem The segment which it supplies occupies the area between the anterior and posterior basal segments and it is overlapped on the medial surface by the medial basal segment on the right side and by the anterior basal segment on the left side Lesions of this segment can be distinguished by their intermediate position from those of the other basal segments

Posterior basal (10) —This is the second of the two terminal branches of the lower lobe bronchus and is actually the continuation of the stem bronchus itself It [illegible]

diaphragm short of the costo-phrenic angle On the left side the shadow is largely obscured by the heart In the lateral view the opacity is triangular with its apex at the hilum and extends downwards and posteriorly to the chest wall and diaphragm

As the posterior basal bronchus represents the terminal part of the primitive stem bronchus, it often has a series of small posterior branches which are the remains of the prominent dorsal series seen in the lungs of lower mammals The apical bronchus of the lower lobe is, of course, the first branch of this dorsal series



(a)

FIG. 12—Consolidation of anterior basal segment of right lower lobe (a) Postero-anterior radiograph of consolidation of right anterior basal segment due to an atypical pneumonia; (b) Lateral radiograph of the same patient.



(b)

The posterior branch immediately below the apical is often quite large described as a separate sub-apical segmental bronchus Individual l sub-segment are sometimes seen but the arrangement of the branches is variable ; in some lungs there is no large sub-apical bronchus and supplied by several smaller branches

BRONCHO-PULMONARY ABNORMALITIES

No account of broncho-pulmonary anatomy would be complete wit mention of the more common abnormalities which may be encounter

Abnormalities of lobation

Additional fissures

It is extremely common to find partial fissures between the broncho-pu segments in addition to the normal inter-lobar fissures The literature numerous examples of so-called supernumerary lobes which prove to be more than segments of the normal lung partially isolated by additional The areas most often affected are the apical segment of the lower lobe medial basal (cardiac) segment Inflammatory conditions of the lung ma thickening of these fissures and render them visible in radiographs as linear sl in the lung, often seen in cases of pleurisy (Fig 13) and pulmonary tuberculosi

Deficient fissures

The normal inter-lobar fissures are often deficient and sometimes absent and Blades (1942) found that the lesser fissure of the right lung was absent in 2 cent of cases and markedly incomplete in 67 per cent , the main fissure wa complete in 30 per cent of both right and left lungs

Fissures due to displaced structures

Lobe of the azygos vein.—This abnormality is too well known to warrar detailed description It occurs in about 0 1 per cent of human right lungs and c sists of a splitting of the right upper lobe by a pleural fold which encloses the azy vein In a postero-anterior radiograph the pleural fold appears as a fine li extending downwards from the apex to the hilum where it terminates in a bulbo shadow caused by the vein itself, sometimes the loop of the vein can be see (Fig 14) The lobe of the azygos vein is merely a part of the normal right uppe lobe and is not an additional structure, the amount of the right upper lobe include in it depends upon the position of the pleural fold and vein (Foster-Carter 1946) It is not usually associated with any other congenital abnormalities

Sequestration of lung due to an abnormal artery.—Sometimes an area resembling one or more broncho-pulmonary segments becomes isolated during development from the remainder of the lung The isolated area is included within the normal pulmonary lobe and is sometimes demarcated by a fissure, but the bronchi within it are usually dilated and cystic and they do not communicate with the remainder of the bronchial tree The condition usually occurs in the lower lobe and is always associated with an abnormal blood supply, the isolated area being supplied by a branch from the thoracic aorta or sometimes by a branch from the abdominal aorta which perforates the diaphragm This abnormality has been called intra-lobar

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FIG 13—Abnormal fissure in the right lower lobe outlined by pleurisy. (*a*) Postero-anterior radiograph G, greater fissure; S, sub-apical fissure between lower apical and posterior basal segments, (*b*) Lateral radiograph of same patient (*By courtesy of Brit J Tuberc.*)

(*a*)

(*b*)

sequestration of the lung by Pryce (1946) who found 5 examples in a se
pulmonary excisions, an incidence of 1 7 per cent It is slightly more co



Fig 14.—Lobe of the azygos vein Postero-anterior radiograph P, pleural fold, V, azygos vein The loop of the vein is well shown (B) courtesy of Brit J Tuberc)

the left side than on the right and it pre-disposes to post-pneumonic sepsis which often leads to its discovery In radiographs, the sequestrated area appears as a dense, sharply demarcated mass which may be mistaken for a localized suppurative pneumonia or a tumour Pryce suggests that traction due to the adventitious blood supply may detach a bulbous tip from the embryonic bronchial tree at an early stage of development and thus cause the broncho-pulmonary abnormality.

Abnormalities of the bronchi

Displaced bronchi

Displacement of the origins of bronchial branches is the commonest abnormality of the bronchial tree We have already mentioned the work of Boyden and his colleagues which has shown that displaced bronchi often pass unrecognized. This is because the basic pattern of the bronchial tree is usually preserved and only detailed analysis will show that some of the branches are not what they seem to be at first sight This abnormality is of importance to the surgeon because the blood vessels are displaced with the bronchus and may be encountered in an unexpected position during operations on the lung Upward displacement of the apical branch of the right upper lobe bronchus is not uncommon and has been mistaken for a supernumerary branch, but the presence of only two branches arising from the upper lobe bronchus is the clue to the diagnosis (Fig 15)—a good example of



(a)

FIG 15.—Displaced apical bronchus of right upper lobe (a) Postero-anterior bronchogram showing apical bronchus (A) arising above the origin of the upper lobe bronchus which has only two branches, anterior and posterior (AL+PL); (b) Lateral bronchogram of same patient (*By courtesy of Brit. J Tuberc.*)

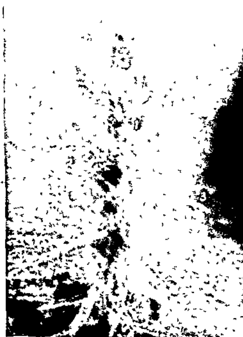


(b)

FIG 16—True supernumerary bronchus in right upper lobe (*a*) Postero-anterior bronchogram showing supernumerary apical branch (S) arising from the trachea, (*b*) Lateral bronchogram of same patient Note that the upper lobe bronchus has its usual three segmental branches (*By courtesy of Brit J Tuberc*)



(*a*)



(*b*)



(a)

Fig 15.—Displaced apical bronchus of right upper lobe (a) Postero-anterior bronchogram showing apical bronchus (A) arising above the origin of the upper lobe bronchus which has only two branches, anterior and posterior (AL+PL); (b) Lateral bronchogram of same patient (*By courtesy of Brit. J Tuberc*)



(b)

CHAPTER 2

APPLIED PHYSIOLOGY OF RESPIRATION

F J PRIME and J MCMICHAEL

ANATOMY

Alveoli

THE ESSENTIAL functioning units of the respiratory system are the alveoli of the lungs Each alveolus is a sac, roughly spherical in shape, measuring 0 08–0·13 millimetre in diameter, whose walls consist of a network of capillaries The total number of alveoli is estimated at 750 million by Zuntz and the combined area of their walls at approximately 55 square metres (Willson, 1922) "Venous" blood from the pulmonary artery is thus spread in a layer about one corpuscle thick over an enormous area, separated only by thin capillary walls from alveolar air, to which it gives up carbon dioxide and from which it absorbs oxygen. No artificial oxygenator used in the physiological laboratory approaches the lungs in efficiency as aerating organs

The tissue elements separating the blood from the alveolar air comprise a single layer of capillary endothelium and a few flattened squames The existence of the latter is denied by some authorities who allege that they appear only as a result of inflammation , others, whilst admitting their existence, are in doubt as to whether they form a complete lining for the alveoli (Willson, 1922) or an incomplete one (Miller, 1947; Josselyn, 1935) In the foetal lung and in certain pathological states the alveoli have a complete lining of cuboidal epithelium From the functional standpoint it is important to realize that the thickness of tissue separating blood from alveolar air is in health very small, and that in disease it may be very much thickened, thus offering a more formidable barrier to the interchange of gases between blood and air

Upper respiratory tract and bronchial tree

In breathing, air is led to the depths of the lungs through the upper respiratory tract, the trachea and the bronchial tree The whole of this conducting system is lined by a membrane containing mucous and serous glands Excepting the oropharynx, the upper part of the larynx and the vocal cords, where the epithelium is stratified squamous in type, the surface epithelium is composed of ciliated columnar cells interspersed with goblet cells The ciliated epithelium is lost in the bronchioles, where it is replaced by a simple cuboidal epithelium Air passing through the upper passages is warmed and moistened, whilst gross particles and bacteria are removed from it before it enters the lungs A rich venous plexus beneath the lining membranes, especially of the nasal passages, gives them the character of an erectile tissue , their thickness and hence the width of the passages is markedly affected by vasodilator activity brought about by heat (Hill, 1935), for example, and by vasoconstrictor substances such as ephedrine, adrenaline and cocaine.

condition may be seen in the bronchial cast shown in Fig 5. Upward displa of the apical branch of the lower apical bronchus also occurs.

Supernumerary bronchi

These are rare and most examples appear to be in the right upper lobe I shows a true supernumerary bronchus arising from the trachea and supplyi of the apical segment of the right upper lobe ; it will be seen that the upp bronchus has its normal three branches

Abnormalities of the lung parenchyma

Accessory lungs

These are isolated masses of rudimentary lung tissue and have been foun in the lower part of the thorax and in the upper abdomen In the former ca mass may be mistaken for an intra-thoracic new growth The condition is more common on the left side than on the right and is often associated congenital defect of the diaphragm. The blood supply of ectopic lungs is from the aorta and Pryce (1946) suggests that they are produced by the mechanism as intra-lobar sequestration

Agenesis of the lung

Rarely, the whole or part of a lung may be absent or represented by only a rudiment. Agenesis of the whole lung is twice as common on the left side as right and three types have been described true aplasia in which there is a main bronchus, cases in which there is a small tracheal diverticulum repres the bronchus to the absent lung, and cases having a rudimentary bronchus le into a small fleshy structure without lobes

BIBLIOGRAPHY

For a general account of the anatomy of the bronchial tree and broncho-pulmor segments, the reader should consult Brock (1947), Foster-Carter (1943) and Fos Carter and Hoyle (1945) The work of Boyden and his colleagues on bronc pulmonary variations is summarized by Boyden (1949).

Boyden, E A (1946) "The Anatomical Hazards of Lingulectomy" *Surgery, St. Louis*, 2
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of the Right Upper Lobe of Fifty Lungs" *Amer. J Anat*, 82, 27
Brock, R C (1947) *Anatomy of the Bronchial Tree* Oxford, Oxford University Press
Ewart, W (1889) "The Bronchi and Pulmonary Blood Vessels" London; Churchil
Foster-Carter, A F (1943) "On the Study of the Bronchi." *Brompton Hosp. Rep*, 1
— (1946) "Bronchopulmonary Abnormalities" *Brit J Tuberc*, 40, 111
— and Hoyle, J C (1945) "The Segments of the Lungs" *Dis Chest*, 11, 511
Kent, E M, and Blades, B (1942) "The Surgical Anatomy of the Pulmonary Lo *J Thorac Surg*, 12, 18
Pryce, D M (1946) "Lower Accessory Pulmonary Artery with Intralobar Sequestrati Lung A Report of Seven Cases" *J Path Bact*, 58, 457
Scannell, J G. (1947) "A Study of Variations of the Bronchopulmonary Segments in th Upper Lobe" *J Thorac Surg*, 16, 530
"Thoracic Society Report on the Nomenclature of Bronchopulmonary Anatomy" (1 *Thorax*, 5, 222.

Blood supply of the lungs

Blood which is to be aerated in the alveoli comes from the pulmonary artery; after leaving the alveolar capillaries it is collected in the pulmonary veins and returned to left auricle The walls of the bronchi receive a separate blood supply from the branches of the bronchial arteries which may arise from the aorta or upper intercostal arteries, but there are frequent irregularities in the origins and number of these vessels, which may also be branches of the innominate, subclavian or internal mammary arteries

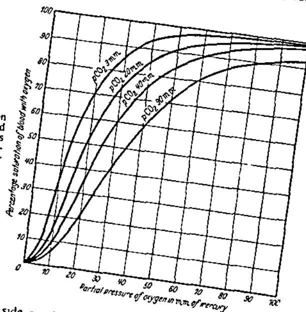


FIG 18—Oxygen dissociation curves of whole blood equilibrated with gas mixtures containing different proportions of CO_2 at 38°C (*after Barcroft*)

Bronchial veins, two on each side, are described which drain from the root of the lung into the terminal part of the vena azygos on the right side and into the left superior intercostal or hemiazygos on the left A point of great importance is that blood in the bronchial veins is collected from a relatively small part of the bronchial arterial distribution According to Miller "except for a limited area at the hilum, all the blood distributed to the bronchial tree is returned by the pulmonary veins".

The anastomosis between bronchial and pulmonary circulations takes place mainly in the capillary bed in the walls of the smaller bronchi and possibly respiratory bronchioles This communication can be of vital importance in assisting the circulation through the alveolar capillaries in cases of congenital cyanotic heart disease In such cases the bronchial arteries, which are quite small in healthy subjects, are sometimes very large They may maintain pulmonary blood flow in other conditions where there is obstruction to the flow in the pulmonary arteries, such as pulmonary embolism and thrombosis,

The trachea and main bronchi are partly surrounded by incomplete rings of cartilage which serve to keep these channels patent; the cartilaginous rings become less and less complete as the bronchi subdivide in the substance of the lung. When these have reached a diameter of about 0 7 millimetre cartilage has disappeared from their walls altogether and they are continued as bronchioles surrounded by zig-zag strands of muscle with elastic fibres and connective tissue. When the muscular coat is lost the bronchioles become continuous with the respiratory bronchioles, in which the first alveoli appear as *diverticula* off the bronchiolar walls Traced distally the respiratory bronchioles end in the alveolar ducts and the atria from which the majority of the alveoli open out (Fig. 17)

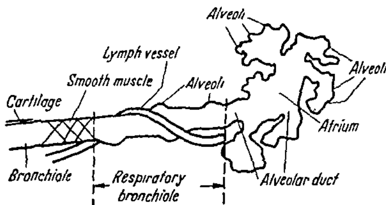


FIG 17 —Schematic representation of lung lobule (*after Miller*)

The muscular tissue of the bronchial tree is chiefly disposed in circular bands, attached to the cartilaginous rings or plates so that their contraction diminishes the calibre of the tubes This is of little moment in the trachea and larger bronchi, but becomes important in the case of the bronchioles, which in some animals such as the guinea-pig, can be closed completely by contraction of the muscle.

The nerve supply to the bronchial musculature is from postganglionic fibres of the cervical sympathetic, which are inhibitor in function, and from vagal fibres running through the pulmonary plexus which cause contraction of the constrictor muscles In man, spasmodic contraction of the bronchiolar muscles is considered to be the immediate cause of asthma, but mucosal swelling with mucus exudation also plays a part

Lymphatic drainage of the lungs

The lymphatics of the lung (Fig 17) form two main groups, a superficial and a deep These communicate in the pleura and at the hila of the lungs. The superficial group originate in the pleura and interlobular septa forming a network covering the surface of the lungs The deep group commence as blind tubes near the beginning of the alveolar ducts (Miller, 1937, Drinker, 1945) and accompanying the bronchi and blood vessels towards the lung root, drain into lymph nodes surrounding the hila of the lungs and bifurcation of the trachea (Miller, 1937)

The partial pressure of carbon dioxide in venous blood provides the pressure head required to transfer it *into the pulmonary alveoli; in venous blood this* pressure is of the order of 45 millimetres of mercury   Thus a difference of pressure of some 6 millimetres of mercury exists between carbon dioxide in alveolar air and that in "venous" blood arriving in the lungs   Oxygenation favours the liberation of carbon dioxide in the lungs, as the partial pressure of carbon dioxide in the blood rises with oxidation of haemoglobin   This mechanism, combined with the lability of carbamino-haemoglobin enables all the excess carbon dioxide picked up by the blood in the tissues to be liberated in spite of the comparatively low pressure difference of carbon dioxide in blood and alveoli

Transport of oxygen in blood

The oxygen carried by the blood is chiefly in loose chemical combination with the haemoglobin of the red cells, about 0 3 millilitre is carried in simple solution in the plasma and cells of 100 millilitres of blood   The volume of oxygen carried by 100 millilitres of normal blood which has been exposed to air until fully oxygenated is about 20 millilitres; this is called the oxygen capacity of the blood In a particular sample of blood not so saturated, the fraction

$$\frac{\text{Oxygen content of sample} \times 100}{\text{Oxygen capacity}}$$

is called the percentage saturation with oxygen   Barcroft and others estimated the percentage saturation of human blood equilibrated with varying known partial pressures of oxygen and used the results to construct the oxygen dissociation curve of the blood   The conditions of the experiment were varied so as to include physiological amounts of carbon dioxide in the gases equilibrated with the blood   In this way a family of curves was prepared which are of physiological importance because they provide the key to the mechanisms of oxygen transport from the alveolar air to the tissues (Fig 18)

Pulmonary artery blood is about 75 per cent saturated with oxygen in the resting state, the carbon dioxide tension in the same sample is of the order of 46 millimetres of mercury   Looking at the curves in Fig 18 it will be seen that the partial pressure of oxygen in blood returning from the tissues to the lungs is about 45 millimetres of mercury   There is thus a wide difference in oxygen pressure between alveolar air and venous blood, amounting to about 50 millimetres of mercury   This pressure head causes oxygen to move rapidly from alveolar air to blood in the alveolar capillaries   These curves show also that at any particular degree of oxygen saturation, the partial pressure of oxygen varies in the same direction as the partial pressure of carbon dioxide   Therefore the liberation of carbon dioxide into the alveoli facilitates the absorption of oxygen from the alveolar air by the red cells   The purely physico-chemical mechanisms underlying the absorption of oxygen and the giving off of carbon dioxide in the lungs are thus beautifully adapted to secure maximum efficiency

In spite of the high speed with which oxygen combines with reduced haemoglobin [illegible]

bronchiectasis and congenital bullous emphysema . surgeons frequently see large bronchial arteries in chronic inflammatory lesions of the lungs like bronchiectasis and tuberculosis,

GAS EXCHANGE IN THE ALVEOLI

At the end of a normal respiratory cycle the lungs contain alveolar air of fairly uniform composition in which the partial pressures of oxygen, nitrogen and carbon dioxide are very close to the partial pressures of those gases in the arterial blood. The percentage composition of alveolar air varies somewhat among individual normal subjects at rest , approximate figures may be listed as follows :

Component	Percentage dry gas	Partial pressure mm Hg
Water vapour	—	48
Oxygen	14 4	100
Carbon dioxide	5 5	39
Nitrogen	80 5	573
Total	100 0	760

In 4 seconds, the duration of a single respiratory cycle in the resting subject, about 330 millilitres of venous blood flow through the lung capillaries During this time the tensions of oxygen and carbon dioxide are altered by the absorption of about 20 millilitres of oxygen and the liberation of a slightly smaller amount of carbon dioxide

While water vapour plays no part in gaseous exchange it is important to keep in mind the total volume of water eliminated by the lungs as vapour, which is almost half a litre a day in ordinary temperate climates

Transport of carbon dioxide in blood

The carbon dioxide carried by blood is in three chemical forms , 5 per cent of it is in simple solution ; about 2–10 per cent in combination with haemoglobin as a carbamino compound and the remainder in the form of bicarbonate in combination with the cations of the plasma (Ferguson and Roughton, 1934) As the haemoglobin becomes oxygenated, that part of the total carbon dioxide which is combined with it is given up At the same time carbon dioxide is liberated from bicarbonate at a rate which is greatly accelerated by the action of carbonic anhydrase, an enzyme present in the red cells (Meldrum and Roughton, 1933) Because carbon dioxide is readily soluble in tissue fluids it can easily diffuse across the alveolar wall , complete equilibrium between the carbon dioxide of the blood and alveolar air is thus secured The actual amount of carbon dioxide given up to the alveolar air depends upon the metabolic activity of the subject and upon the chemical nature of the substances metabolized ; normally it is about 200 millilitres per minute in a resting adult

By no means all the carbon dioxide of the venous blood is given off in the lung. A large amount, about 50 millilitres per 100 millilitres of blood, is retained and, in the form of bicarbonate, it plays an important part as a buffer substance.

pO_2 of a blood sample undergoes considerable changes with temperature, and that living cells (leucocytes) in the blood consume significant amounts of dissolved oxygen during any delay in handling. Quite apart from the errors in determination of arterial pO_2 is the other difficulty of determining the pO_2 of alveolar air. Sonne, Roelsen and others have shown by taking samples of alveolar air during different phases of expiration that differences of oxygen content in samples of alveolar air exist which are large enough to make the determination of the pressure gradient between arterial blood and alveolar air a matter of uncertainty. The general consensus of opinion is that the arterial pO_2 is somewhat lower than the alveolar pO_2 and that the difference between them (written ΔpO_2) is in the range of 5–10 millimetres of mercury.

Oxygen unsaturation of arterial blood

The reasons advanced for the normal unsaturation of arterial blood are:

(a) The alveolar ventilation in the normal subject is not uniform; that the pO_2 in some alveoli is sufficiently low to reduce the completeness of oxygen saturation. Alveoli which contain oxygen at a higher partial pressure than 100 millimetres cannot raise the saturation of the haemoglobin in the blood perfusing them very much (Fig 18), whilst blood exposed to alveolar pO_2 less than 80 millimetres of mercury may be considerably suboxygenated.

(b) Blood leaving the alveolar capillaries may be in fact fully saturated but it is diluted during passage to the heart by the addition of blood from the bronchial veins and again in the left heart by the further addition of venous blood from some of the Thebesian veins which drain the myocardium.

(c) It is considered by some authorities that blood leaving alveolar capillaries is not in complete equilibrium with the alveolar air to which it has been exposed because, unlike carbon dioxide, the low solubility of oxygen in tissue fluids interferes with the speed of diffusion across the membrane separating blood and air.

REGULATION OF RESPIRATION

Nervous control of breathing

The resting subject is hardly aware of respiratory movements which are carried out reflexly in response to stimuli acting upon the respiratory centre.

The respiratory centre consists of a group of nerve cells, the lower end of which lies superficially near the upper end of the medulla oblongata, it extends upwards into the pons and is said to have fibre connexions with nuclei in the pons and brain stem (Ranson, 1943). It is not relevant to the present discussion to describe the arrangement of pathways within this centre, the external connexions, however, deserve mention.

Afferent impulses are conveyed to the respiratory centre from the cerebral cortex, the lungs, carotid and aortic reflexes and from other afferents.

The cerebral cortex

Impulses arising here enable respiratory rhythm voluntarily to be varied as required, for example in talking, breath-holding. Emotions such as fear, surprise and amusement also alter respiratory rhythm through cortical activity.

with a partial pressure (pO_2) of somewhere near 90 millimetres of mercury. Much disagreement exists between experts upon the magnitude of this difference in partial pressures. Barcroft and Bock, for example, estimated the pO_2 of arterial blood at 85 millimetres of mercury. Other workers maintain that it is nearly 100 millimetres of mercury (Comroe and Dripps, 1944) The difference of opinion arises as a result of the technical difficulty of determining the pressure of oxygen (pO_2) in a sample of blood One method used by Barcroft and in a

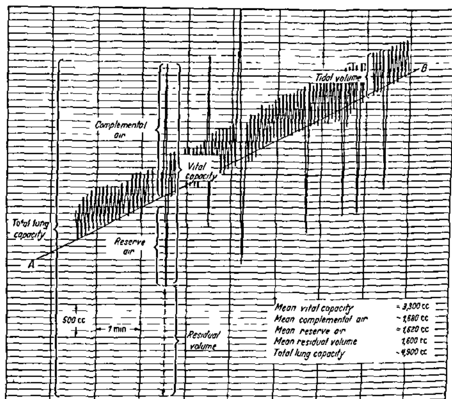


FIG 19 —Normal spirogram showing the subdivisions of total lung capacity AB represents the rate of absorption of oxygen from the lung spirometer system

modified form by Riley and others is to equilibrate a small bubble of air with a large excess of blood in a syringe kept at body temperature After equilibration the bubble is analysed This is essentially the same technique as that used by Krogh in animal experiments many years ago and is theoretically very good Errors arise, however, in manipulating so small a volume of gas, which are sufficiently large to create real difficulties of interpretation Another method is the polarographic estimation of pO_2, used by Berggren (1942) This method seems to be promising but there are still great technical difficulties in its use on blood Whatever instrumental accuracy is achieved it should be remembered that the

The lungs

Special receptors thought to be situated in the walls of the alveolar ducts are susceptible to stretch and compression. These give rise to afferent fibres running in the vagus nerves which limit both inspiration and possibly also expiration. Reflexes originating in these end organs were first described by Hering and Breuer in 1868, who showed that inflation of the lungs inhibited inspiration and initiated expiration whilst deflation inhibited expiration and brought on inspiration. Ablation of the pulmonary fibres of the vagi in the experimental animal results in deeper and slower breathing

Carotid and aortic reflexes

The pressoreceptors situated in the walls of these vessels inhibit respiration when stimulated by a sharp rise of intravascular pressure. There is no evidence that this reflex is of any clinical importance Chemoreceptors, which seem to be situated in the carotid body (Schmidt and Comroe, 1940), are of importance because they are susceptible to changes in oxygen tension ; when this reaches the low level of 70 millimetres of mercury, discharges pass centrally which cause breathing to become deeper and more rapid The chemoreceptors are much less susceptible to changes in carbon dioxide tension than is the medullary respiratory centre itself (Schmidt, Dumke and Dripps, 1939)

Other afferents

Pain usually increases the respiratory rate, though the response to pain may be masked by the response to other afferent impulses arriving at the respiratory centre at the same time, as well as by the prevailing chemical environment of the cells of the respiratory centre (Gesell, 1939)

By far the most important mechanism for controlling the volume of ventilation is the chemical one Haldane and Priestley (1935) drew attention to the sensitiveness of the respiratory centre to changes in arterial pCO_2 They found that a rise of 1·5 millimetres of mercury was sufficient to double total ventilation ; this corresponds with a rise of carbon dioxide content in the alveolar air of only 0 2 per cent

Action of carbon dioxide on respiratory centre

The manner in which carbon dioxide acts on the respiratory centre has been a subject of debate in recent years Two views are held ; one, that carbon dioxide has a specific stimulating effect on the centre, the other that carbon dioxide acts by raising the hydrogen ion concentration of the blood supplying the centre Increased acidity of the blood does, in fact, stimulate respiration, as is clinically apparent in acidosis due to diabetes or the terminal phases of chronic nephritis, but for a given range of *p*H, the effect of solutions of carbonic acid is greater than that of any other acid The specificity of carbon dioxide as a respiratory stimulant, however, is still not finally accepted by all authorities

The next most important substance in the chemical control of respiration is oxygen It is now generally accepted that anoxia depresses the medullary respiratory centre. breathing becoming shallower and less frequent as anoxia

which actually reaches the alveoli of the lungs It has already been pointed out that alveoli do not occur in the bronchial tree until the respiratory bronchioles are reached Above these, at the end of expiration is a non-respiring space filled with alveolar air. The next intake of air washes this back into the lung, together with a volume of air which, added to the dead space air, is equivalent to the tidal air This volume of air is called the *effective tidal air* (tidal air—dead space = effective tidal air)

Now it is clear, that to be effective, the tidal air must exceed the dead space If it does not do so, no matter how rapidly the subject breathes, no fresh air will reach the alveoli and he will have to rely on gaseous diffusion only in order to secure adequate gas exchange between the alveoli and the atmosphere In man the volume of the anatomical dead space is estimated at about 170 millilitres Haldane (1900) has shown that in pneumonia, where respiration is rapid and shallow, severe and may be fatal anoxia could result His findings have been underlined by the work of Birath (1944) who has shown that in some diseases, especially in emphysema, the volume of what is functionally " dead space " may be more than double the normal value Reference to this subject will be made later when mixing of gases in the lung is discussed

Vital capacity—Certain measurements may be made spirographically which are of great importance in determining the mechanical efficiency of what may be called the " bellows function " of the lungs First among these is the vital capacity This is the largest volume of air which can be expelled from the lungs following a maximum inspiration (Fig 19) The amount of air inhaled during a maximum inspiratory effort is called complemental air (inspiratory capacity), that is the amount of additional air required to distend the lungs as far as possible from the resting level. The amount of air which can be voluntarily squeezed out of the lungs at the end of a normal expiration is the reserve air (expiratory reserve volume) These may be recorded separately and added together to give the vital capacity instead of recording the whole at one time When calculated in this way the result is sometimes slightly higher than in the single measurement As might be expected, patients whose lungs are fibrotic show this difference more obviously and commonly than do normal individuals

The importance attached to this measurement in clinical work arises from the ease with which it can be made Until quite recently it was the only measurement used to assess pulmonary bellows function It must be realized, however, that the vital capaci[illegible]
istics of the lun[illegible]
more, the size [illegible]
many of which are only indirectly concerned in respiration Anything which [illegible]
[illegible]
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due to pleurisy may limit vital capacity severely, as may muscular weakness due to nervous disorder, such as subacute combined degeneration, hemiplegia or poliomyelitis Diseases affecting the structures of the chest wall such as scleroderma, ankylosing spondylitis and kyphoscoliosis must also appear in a list of conditions lowering vital capacity

Spirography

A record may be made of movements of air in and out of the lungs by means of a spirometer. Such a record, called a spirogram, is essential in investigating respiratory insufficiency and affords a useful starting point for a discussion of the physiological aspects of breathing A typical spirogram from a normal healthy adult is shown in Fig 19

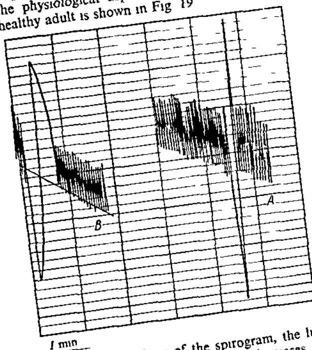


FIG 20—(A) Kymographic record of normal breathing and vital capacity. (B) Similar tracing from a subject suffering from bronchial asthma Note the prolonged time taken to give full vital capacity.

During the making of the spirogram, the lungs of the patient and the spir meter form a closed circuit which decreases in volume due to consumption oxygen by the patient while carbon dioxide in the expired air is absorbed by canister filled with soda lime in the spirometer This steady decrease in volu is reflected in the spirogram by the uniform upward slope of the tracing, mar by the line AB The oscillations of the tracing above the line represent movements of the tidal air (volume), an upward stroke for inspiration an downward for expiration Suitable calibration marks on the paper enable observer to measure the volume of the tidal air on a vertical scale and the dura of the tracing on a horizontal scale The product of the mean volume of air and the number of breaths taken during 1 minute gives the *total ventil* or *minute volume respired*, usually expressed in litres per minute. The air is moved in and out of the lungs by alterations in their capacity br about by expansion and collapse of the thorax.

Importance of dead space of lungs.—Factors affecting the total ventilation already been considered There is one further point which requires em here Total ventilation may be raised either by an increase in the rate depth of breathing or both It is obvious that the volume of tidal ai volume) registered spirographically does not represent the volume of fr

Several methods of estimating residual air are available. In one method the lungs are connected to a spirometer to form a closed system. A measured volu[me] of a foreign gas, such as helium, is introduced into the system, after a per[iod] of rebreathing during which mixing takes place between the gases in the spi[ro]meter and the lungs, the degree of dilution of the added gas is measured. Fro[m] this figure the volume of the lung spirometer system may be calculated, th[e] initial volume of the spirometer being known, the volume of air in the lungs may be estimated by subtraction (McMichael, 1939). A second method is that of Darling, Cournand and Richards (1940), in which the nitrogen content in the lung air is washed out during a 7-minute period of breathing pure oxygen. Analysis of the expired air collected throughout this time enables the volume of nitrogen originally present in the lung to be determined, and from this an estimate may be made of the volume of air in the lung. These methods have been found to give comparable results, the first, however, permits the use of a simple electrical gas analyser, which makes it both quicker and simpler, and allows the simultaneous recording of the rate of mixing of the foreign gas with the lung air to be measured.

The ratio of residual air to total lung capacity is one of the most important figures obtained from this investigation. It has been shown by several workers that in a given individual this ratio is fairly constant (Hurtado and Boller, 1933, Hurtado and Fray, 1933, McMichael and Herrald, 1939). Normally it is about 28 per cent of total lung capacity with a standard deviation of ± 6 per cent; values over 40 per cent, therefore, are almost certainly abnormal, though the values tend to rise with advancing age. It is easy to understand that the ratio of residual air to total lung capacity will be high in gross emphysema and figures up to 80 per cent may be encountered.

It is important, however, to remember that various conditions which reduce total lung capacity, such as pulmonary fibrosis or pulmonary engorgement in heart failure are accompanied by an increase in this ratio. The ratio may also be disturbed temporarily by asthma. It cannot, therefore, be accepted by itself as a diagnostic criterion of emphysema. In cases of doubt, examination of the general form of the spirogram may help, for example, in emphysema the graphic record of vital capacity is quite characteristic, having a markedly rounded outline at either end indicating a slow and prolonged effort to inhale or expel air at the limits of a deep breath. Such a spirogram is shown in Fig 20.

Dynamics of respiration.—The foregoing descriptions, with the exception of minute volume respired, have been concerned with what are termed by Moncrieff "anatomical measurements", in order to distinguish them from dynamic measurements more closely allied to the actual performance of the lung bellows. Minute volume respired is a record of respiratory performance when the subject is in a steady state of rest, sitting in a chair or propped up in bed. By contrast, maximum breathing capacity is the volume of air respired per minute when the subject breathes voluntarily as deeply and rapidly as he can for a short period. In practice, the best way of making the measurement is to get the subject to breathe in and out of a simple spirometer without valves and without absorption of carbon dioxide. The movements of the spirometer may be recorded by an electrical device similar to a revolution counter or graphically on a revolving

Prediction of vital capacity.—When in 1846, Hutchinson published his investigations on vital capacity, he derived from his results a simple rule relating the height of his subjects to their vital capacity. In doing this he introduced an idea which is of great importance in clinical studies of respiration, namely, using the patient's own body measurements as data for predicting normal expected results. These predicted measurements are used to compare with those actually found. In modern practice normal standards are based on measurements of surface area (Dreyer, 1914; West, 1920) or stem height (Dreyer, 1919, 1920) or "radiological chest volume" (Fray, 1935), a measurement based on chest area in a radiograph and antero-posterior depth of the chest. Two prediction formulae are given below.

1. $\left(\frac{\text{Weight in grammes}}{0.690}\right)^{\cdot 72}$ = vital capacity (Dreyer, 1920)
2. (a) Height cms × 27.63 − (0.112 × age yrs.) = vital capacity (males)
   (b) Height cms × 21.78 − (0.101 × age yrs.) = vital capacity (females).
   (Cournand *et al*, 1948)

It must be added that according to a critical analysis of all the published data by Cripps (1924), none of the prediction formulae then in use gave results "confined within sufficiently narrow limits to possess any real prognostic value in individual cases."

Hitherto it has been the custom in clinical practice to measure vital capacity with a simple spirometer without making a tracing of the performance. Additional information may be obtained from a tracing, however, so that it is always advisable to have it. Not only is it possible to read the subdivisions of vital capacity from the record of the resting respiratory level which it provides but also the general pattern of the vital capacity may be seen. In order better to appreciate this point 2 tracings (Fig. 20) are shown of vital capacities which are of about equivalent size, one from a healthy subject, the other from a patient who suffered from chronic bronchitis with an added element of bronchial spasm. It will be noticed that the upward and downward strokes of the tracing on the right, from the healthy subject, are nearly vertical for the whole of their length, indicating a rapid and easy performance, whilst in the other, the vertical parts of both upward and downward strokes are about half of the total lengths; thereafter both lines slope away from the vertical more and more, indicating a progressive slowing-up of air flow into and out of the lungs. The contrast in pattern is significant because it implies that the useful range of vital capacity available for deep and rapid breathing may be more restricted in the second case than the simple figure for vital capacity might lead the observer to expect.

Residual air and total lung capacity.—The observations relating to the "lung bellows" mentioned so far are made directly from the spirogram. There remains to be described the measurement of residual air. This is the amount of air which still remains in the lungs after a maximal expiration. The following relationships define two other terms not yet described which are important.

Residual air + vital capacity = Total lung capacity
Residual air + reserve air = Functional residual air

These are also shown diagrammatically in the normal spirogram (Fig. 20). These figures provide all the physical dimensions of the lungs.

limited range there is a linear relationship between total ventilation per minu[te] and work done by the subject In the grossly abnormal cases where dyspnoe[a] of effort is experienced, maximum ventilation occurs earlier than in norma[l] subjects, and it may be greater in relation to the exercise undertaken Cournan[d] and others have found that dyspnoea is present when total ventilation is about 40 per cent of the maximum breathing capacity This is the case whether the patient is exercising or not Consequently in a subject in whom the maximum breathing capacity is severely restricted, exercise tolerance is also restricted As a measure of the degree of disability in this respect the idea of breathing reserve has been adopted, this is the difference between resting ventilation per minute and maximum breathing capacity, and is usually expressed as a percentage of the maximum breathing capacity In the healthy subject breathing reserve is nearly 90 per cent of the maximum breathing capacity In subjects who have hardly any breathing reserve the percentage may be as low as 60 per cent, in which case dyspnoea is present at rest

Intrapulmonary mixing.—It has been mentioned already that to secure an adequate alveolar oxygen tension, even distribution of inspired air throughout the lungs is necessary The theory of intra-pulmonary mixing has been considered by several writers (Cournand, 1944, Bateman, 1945, Birath, 1944) who have tested their hypotheses experimentally Knowing the dead space of the lungs and the functional residual air it is possible to calculate the rate at which the nitrogen content of the expired air will decrease as the subject breathes pure oxygen Cournand and his colleagues (1944), assuming uniform ventilation, calculated what should be the nitrogen content after a given number of breaths and compared this with the experimental findings, they concluded that in the normal subject intrapulmonary mixing was nearly perfect They also showed that in emphysematous subjects varying degrees of inadequate mixing were present This technique has been extended by other workers (Birath, 1944, Bateman, 1945) who in the main have confirmed Cournand's results

Birath measured the dead space of the lungs and found that in emphysema and in tuberculosis and several other affections of the lungs the apparent dead space was increased from the normal His calculations which gave dead space are really a measure of the inefficiency of mixing and are not strictly related to any fixed concept of dead space

Dead space (trachea and air passages) may be regarded as ventilated space with no respiratory function Briscoe, Becklake and Rose (1951, 1952), have more recently made measurements of spaces in the lungs with respiratory function but poorly ventilated One can imagine normal alveoli with bellows movements in which ventilation is adequate and blood in the walls fully aerated Alongside these in some abnormal conditions there may be spaces in which practically no bellows movement is taking place and where blood perfusing the walls is inadequately aerated Such poorly ventilated space can be recognized and measured approximately by the study of the rate at which an inhaled foreign gas (helium) approaches its final equilibrium concentration in the lungs In normal subjects there is hardly any poorly ventilated space and mixing of inhaled gas in the lungs is rapid In emphysematous subjects poorly ventilated space may exceed 2 litres and the existence of this space seriously impairs the

…cases the tidal air and hence the minute ventilation are only slightly decreased This observation would seem to indicate that there is a larger quantity of blood flowing through the lower lung, possibly due to a gravity effect in the case of posture, though this explanation will not hold in the case of the fixed hemithorax

In disease, especially in disease of the pleura, oxygen consumption from the affected lung may be completely abolished, but movements of the lung are little affected The accompanying bronchospirogram (Fig 21) was taken from a patient who had a left-sided tuberculous pleurisy of some standing and shows this effect Calculation of the ventilation equivalents for oxygen underlines the inadequacy of this measurement on the normal spirogram In the case mentioned the ventilation equivalent for oxygen calculated from the spirogram made in the ordinary way was 2 3 The ventilation equivalent for the right lung, however, was found to be 6, which is grossly above normal, whilst that of the left lung was 1·2, which is lower than normal

It has also been found by Whitehead, O'Brien and Tuttle (1942) that administration of pure nitrogen to one lung caused the other lung to take up a much larger quantity of oxygen per minute, thus compensating for the anoxia Whitehead also found during this experiment that oxygen was actually given up by the blood in the lung ventilated with nitrogen, a finding which is to be expected in view of the existing oxygen content of the blood perfusing it Carbon dioxide output from the 2 lungs is affected in a somewhat similar way to that of oxygen but it is quite common to find that a lung which is not absorbing oxygen may be putting out a certain amount of carbon dioxide provided it is ventilated

Amongst the disadvantages of bronchospirometry is the fact that it cannot be employed in cases where the patients have a lot of sputum, because of the risk of blocking the catheters It is also desirable that the patients should be conscious during the procedure so that recordings of vital capacity may be made, since even with the most perfect anaesthesia the procedure is not a particularly comfortable one and is not even entirely free from danger, its use is somewhat limited

An absolute contra-indication to the procedure exists in those cases where the naso-pharynx or the vocal cords are affected by any inflammatory disease which might be spread into the lungs by the passage of a bronchial catheter

Quite apart from these contra-indications, information given from bronchospirometry is not often clinically helpful Surgeons frequently consider that they may deduce from the results of bronchospirometry an answer to the question whether a given lung should be removed or not. That bronchospirometry does not answer this question will be fairly clear to anyone who has followed this account of the physiology of respiration thus far There is good evidence that removal of one lung is largely compensated by increased function of the other and no doubt this has saved the lives of many patients who have had thoracic operations without benefit of complete investigation Also, it must be realized that bronchospirometry measures only the bellows function of the 2 lungs and this we have seen is only part of the information necessary to the building up of a complete picture of respiratory function in a given case At present, therefore, bronchospirometry must be used with caution to give information which cannot be obtained in any other way, and the results may be found to be disappointingly conclusive

efficiency of lung ventilation The concept of "poorly ventilated alveoli" represents an important idea which should clarify many of the old controversies surrounding the concept of "dead space"

Oxygen consumption—In any discussion of respiratory function the question of exercise tolerance is of ultimate importance. The ability to meet the demand for oxygen made by the tissues under all conditions is the mark of an efficient respiratory system This places in its correct perspective the intimate relationship between the lungs and the cardiovascular system The functional integrity of both of these is necessary in order to secure an adequate environment in which tissue cells can work Anthony (1930) discussed this question and introduced the idea of the ventilation equivalent, which is the pulmonary ventilation required to absorb 100 millilitres of oxygen In the resting normal subject he found the value of this to be about 2 3 litres with a rather wide scatter. It is true that in severe emphysema the value of the equivalent may be raised considerably ; values of 5 and 6 are not unusual, but the variability of both these equivalents is such as to make their use rather limited. One of the reasons for this has appeared as the result of broncho-spirometric studies where it has been found that patients who have a ventilation equivalent for oxygen which is nearly normal when measured by ordinary spirometric means may have a ventilation equivalent for oxygen of less than 2 in one lung and more than 6 in the other (Fig. 21)

Bronchospirometry

This is a method of recording the movements of the two lungs separately and simultaneously and of comparing the rate of gas exchange occurring in them Introduced by Bjorkmann in 1934, it has not been used very widely in Great Britain Bjorkmann designed a special bronchoscope equipped with suitable rubber cuffs, the end of which he passed into the left main bronchus under direct vision , the bronchoscope had two channels, one which continued to the end of the instrument which was lodged in the bronchus and one which opened in the trachea By inflating the rubber cuffs, the two openings were sealed off from each other so that air entering and leaving either lung did so only through the appropriate channel ; the tracheal opening communicated with the right lung A more convenient rubber catheter, having two channels and inflatable cuffs has been designed by Zavod (1940) , this is more often used now than the bronchoscope

All the measurements previously described for the ordinary spirogram are made on the two spirograms given by this method A check may be made of the adequacy of the readings by adding together the vital capacities of the two lungs separately and comparing the result with the total vital capacity estimated immediately before or after the test

Among the interesting things which have been observed are the following Oxygen consumption is slightly different in the two lungs, the right lung absorbing approximately 54 per cent of the total oxygen consumption This is perhaps not surprising when the relative sizes of the two lungs are remembered What is more interesting, however, is the effect of posture upon oxygen consumption. [illegible]

should be remembered that in patients who are chronically anoxic (emphysema) the respiratory centre is no longer sensitive to carbon dioxide (Scott, 1920) Under these circumstances anoxia itself becomes an important stimulus in the maintenance of pulmonary ventilation Oxygen administration may depress respiration, and cause retention of carbon dioxide in the tissues with deleterious results Inhalation of high percentages of carbon dioxide raising the tissue pressure of carbon dioxide may induce narcosis even in previously healthy subjects

BIBLIOGRAPHY

Anthony, A J (1930). "Untersuchungen uber lungen volumina und lungen ventilation." *Dtschs Arch. Klin Med*, **167**, 129

— (1937) *Funktionsprufung der Atmung*, Leipzig

Baldwin, E de F, Cournand, A, and Richards, D W (1948–49) "Pulmonary Insufficiency A study of 39 cases of pulmonary fibrosis" *Medicine*, **27**, 243, **28**, 1

Barcroft, J (1914) *The Respiratory Function of the Blood* London, Cambridge University Press

Bateman, J B (1945) "The Measurement of Intrapulmonary Mixing and Pulmonary Insufficiency" *Proc Mayo Clin*, **20**, 13

Berggren, S M (1942) "The Oxygen Deficit of Arterial Blood caused by Non-ventilating Parts of the Lung" *Acta Med Scand*, **4**, Suppl xi

Birath, G (1944) "Lung Volume and Ventilation Efficiency" *Acta Med Scand*, **4**, Suppl 154

Bjorkmann, S (1934) "Bronchospirometrie" *Acta Med Scand*, Suppl 56

Briscoe, W A, Becklake, M R, and Rose, T F (1951) "Intrapulmonary Mixing of Helium in Normal and Emphysematous Subjects" *Clin Sci*, **10**, 37.

Comroe, J H, Jun, and Dripps, R D, Jun (1944) "The Oxygen Tension of Arterial Blood and Alveolar Air in Normal Human Subjects" *Amer J Physiol*, **142**, 700

Cournand, A, and Richards, D W (1941) "Pulmonary Insufficiency Discussion of physiological classification and presentation of tests" *Amer Rev Tuberc*, **44**, 26

— — and Lassen, H C A (1937) "Pulmonary Insufficiency Discussion of physiological classification and presentation of tests" *J Clin. Invest*, **16**, 1

Cripps, L (1924) "Application of the Air Force Physical Efficiency Tests to Men a. Women" *Spec Rep Ser Med Res Council*, No 84

Darling, R C, Cournand, A, and Richards, D W (1940) "Studies on the Intrapulmonar Mixture of Gases" *J Clin Invest*, **19**, 609

— — Dickinson, A, and Richards, D W (1944) "Studies on the Intrapulmonary Mixtur of Gases" *J Clin Invest*, **23**, 55

Davies, C E, and Mackinnon, J (1949) "Neurological Effects of Oxygen in Chronic Cor Pulmonale" *Lancet*, **2**, 883.

Donald, K W (1947) "Oxygen Poisoning in Man" *Brit med J*, **1**, 712

Dreyer, G (1919) "The Normal Vital Capacity in Man and its Relation to the Size of the Body" *Lancet*, **2**, 227

— (1920) *Assessment of Physical Fitness*, London

— and Burrell, L S T (1920) "The Vital Capacity Constants applied to the Study of Pulmonary Tuberculosis The Importance of these Constants as a Guide to Classification and as a means of Ascertaining the Results of Treatment" *Lancet*, **1**, 1212

Drinker, C K (1938) *Carbon Monoxide Asphyxia* Oxford, Oxford University Press

— (1945) *Pulmonary Edema and Inflammation* Cambridge, Mass, Harvard University Press

Fenn, W O, Rahn, H, and Otis, A B (1946) "A Theoretical Study of the Composition of the Alveolar Air at Altitude" *Amer. J Physiol.*, **145**, 637

Ferguson, J H W, and Roughton, F J W (1934) "The Direct Chemical Estimation of Carbamino Compounds of CO_2 with Haemoglobin" *J Physiol*, **83**, 68.

— — (1934) "The Chemical Relationships and Physiological Importance of Carbamino Compounds of CO_2 with Haemoglobin" *J Physiol*, **83**, 87

Fray, W. W (1935) "Roentgenological Study of Pulmonary Ventilation. Method for prediction of normal pulmonary capacities based upon Roentgen measurements" *Amer J Roentgenol*, **33**, 2

When total pneumonectomy is being considered it is important to be satisfied that the remaining lung will function adequately in the absence of its neighbour. A decisive answer in cases of doubt may possibly be provided by the technique of Hanson and Carlens (1951) A cardiac catheter with a small inflatable balloon near its tip can be passed through the right heart into the right or left pulmonary artery Temporary inflation of the balloon in this situation deflects the entire cardiac output through the opposite lung which then takes the whole burden of haemo-respiratory exchange : the reaction of the patient can then be observed. On occasions this somewhat drastic test may be fully justified as a preliminary to the even more drastic and irreversible test of pneumonectomy.

SOME PROBLEMS OF OXYGEN AND CARBON DIOXIDE ADMINISTRATION

Quite apart from diseased conditions men are nowadays subjected to extreme physiological strains in high flying and deep diving Rapid ascent, whether from the depths of the sea or into the air, leads to sudden decompression with the escape of dissolved nitrogen as bubbles in the blood stream and consequent symptoms of caisson disease or decompression sickness. Breathing pure oxygen at atmospheric pressure before the ascent is made will wash out a large amount of the dissolved nitrogen from the blood enabling rapid ascents to be made.

In aeroplanes flying above 10,000 feet oxygen apparatus is provided which obviates the insidious ill effects of oxygen lack on cerebration. While inhalation of oxygen at low atmospheric pressure overcomes some of the difficulties it becomes quite useless at a height of 50,000 feet. At this level the necessary carbon dioxide and water vapour pressures in the alveoli become nearly equal to the total atmospheric pressure (Fenn, Rahn and Otis, 1946). Pressurized cabins are therefore needed at these exceptional altitudes.

The administration of pure oxygen at high pressure to submerged divers also leads to difficulties High partia[illegible] interfere with the carriage of carbon dioxi[illegible] blood will carry more carbon [illegible] At high oxygen pressures brain metabolism is impaired as certain important enzymes are put out of action (Donald, 1947). At pressures of 3–4 atmospheres of oxygen, convulsive seizures may be induced. Such pressures are encountered at a depth of 15 fathoms (3 7 atmospheres)

In the subjects of chronic anoxia (for example, severe emphysema) the administration of oxygen by oxygen tent at atmospheric pressures may lead to mental confusion and convulsions (Davies and Mackinnon, 1949) It would appear that the physiological adaptations to low oxygen tension create an intolerance of sudden change to higher partial pressures of oxygen The nature of these reactions is still uncertain but as a practical rule the reaction of each patient with pulmonary anoxia must be carefully watched during oxygen administration It may be better to have a patient blue and talking than pink and unconscious. Carbon dioxide is frequently used as a stimulant where the respiratory centre is depressed under various anaesthetics Seven per cent carbon dioxide in oxygen is also recommended by Drinker (1938) for treatment in carbon monoxide poisoning. It

CHAPTER 3

ACUTE TRACHEO-BRONCHITIS

J. G SCADDING

ACUTE inflammation of the trachea and bronchi occurs in many forms They will be classified for purposes of description as follows (1) Of uncertain or mixed aetiology (a) Acute catarrhal tracheo-bronchitis ; (b) Acute laryngo-tracheo-bronchitis of infants , (c) Acute suppurative bronchitis , (d) Acute fibrinous or plastic bronchitis (2) Associated with specific infections (3) Associated with dust inhalation (4) Due to inhalation of noxious gases

ACUTE CATARRHAL TRACHEO-BRONCHITIS

Aetiology

Acute catarrhal tracheo-bronchitis is usually due to descending infection from the upper respiratory tract It is thus often related to common colds and epidemic febrile catarrhs, which are presumably of virus origin , but in some cases no relation to such infections can be detected

The factors which determine the occurrence of acute bronchitis, even after an upper respiratory infection, are not clearly defined Certain epidemics of "febrile catarrhs" show a peculiar tendency to give rise to cases of bronchitis, although whether these are due to specific infecting agents remains unknown At the extremes of life, bronchitis is more frequent, and often presents special features rendering it then a much more grave condition Cold damp weather predisposes to the development of bronchitis after upper-respiratory infections

Pre-existent damage in the bronchi or lungs, such as bronchiectasis or chronic tuberculosis, predispose to it Persons suffering from cardiac disease, especially mitral stenosis, or from renal disease, seem to be more prone to attacks of bronchitis , it is doubtful whether there is an increased liability in these patients, or whether mild attacks, which would cause no troublesome symptoms in normal persons cause more noteworthy symptoms in them Finally, certain individuals, even without detectable abnormalities in the lower respiratory tract, show a predisposition to acute bronchitis , it seems that, in these subjects, bronchitis forms part of the pattern of the common respiratory epidemic infections This predisposition is sometimes familial, and may be associated eventually with the development of chronic bronchitis and emphysema The possible inter-relations of bronchitis and the allergic group of diseases, as well as the influence of dusts in causing bronchitis, are discussed below

Bacteriology

Bacteriological studies in this apparently non-specific bronchitis usually yield little useful information *Streptococcus viridans*, non-haemolytic streptococci, *M. catarrhalis*, *H influenzae*, *N pharyngis*, and occasionally *Str. haemolyticus*, pneumococci or staphylococci may be present in the sputum , but, with the

Gebauer, P. W (1939). "A Catheter for Bronchospirometry." *J. Thoracic Surg.*, **8**, 674.
Gesell, A (1939). "Respiration and its Adjustments" *Amer Rev. Physiol*, **1**, 185.
Haldane, J S (1900) "The Ferricyanide Method of Determining the Oxygen Capacity of the Blood" *J Physiol*, **25**, 295
— and Priestley, J. G (1935). *Respiration* Oxford; Clarendon Press
Hansen, J., and Carlens, P. (1951) Communication to the Thoracic Society, 23rd February.
Hartridge, H, and Roughton, F J W (1923) "The Velocity with which Carbon Monoxide Displaces Oxygen from Combination with Haemoglobin" *Proc. Roy. Soc.*, B, **94**, 336
Hering, E, and Breuer, J (1868) "Die felbststenerung der athmung durch den nervus vagus" *Sitzungsb Anad Wissensch Wien*, **56**, 672; **58**, 909
Hill, L. (1935). "Narrowing of the Air Tubes of the Lung produced by Close Warm Conditions." *J. Physiol*, **85**, 17.
Hurtado, A, and Boller, C (1933). "Studies of Total Pulmonary Capacity and its Subdivisions" *J Clin Invest*, **12**, 793
— and Fray, W W (1933a) "Studies of Total Pulmonary Capacity and its Subdivisions." *J. Clin Invest*, **12**, 807
— — (1933b) "Studies of Total Pulmonary Capacity and its Subdivisions III Changes with Body Posture" *J Clin Invest*, **12**, 825
— — Kaltreider, N L, and Brooks, W D W (1934) "Studies of Total Pulmonary Capacity and its Subdivisions V Normal Values in Female Subjects" *J. Clin Invest*, **13**, 169
— — — — and McCann, W S (1934) "Studies of Total Pulmonary Capacity and its Subdivisions" *J Clin Invest*, **13**, 1027
Hutchinson, J (1846) "On the Capacity of the Lung and in the Respiratory Functions with a View to Establishing a Precise and Easy Method of Detecting Disease by the Spirometer." *Med Chir., Trans*, **29**, 137
Josselyn, L E. (1935) "[illegible]" *Anat Rec*, **62**, 147.
McMichael, J (1939) [illegible]
— and Herrald, F [illegible] a simple constant [illegible] 491.
[illegible] 309
[illegible] "Carbonic Anhydrase [illegible] its preparation and [illegible]
[illegible] Thomas
Moncrieff, A (1934) "*Tests for Respiratory Efficiency*" *Spec Rep Ser Med Res Coun*, 198
Peters, J. P, and van Slyke, D D (1932) *Quantitative Clinical Chemistry*, Vol 2 Baltimore, Williams and Wilkins
Pinner, M, Leiner, G, and Zavod, W A (1942) "Bronchospirography" *Amer. J. Thor Surg*, **11**, 241.
Ranson, S W (1943) *Anatomy of the Nervous System* Philadelphia; Saunders
Riley, R. L, Proemmel, D D, and Franke, R E (1945) "A Direct Method for the Determination of Oxygen and Carbon Dioxide Tensions in Blood" *J. Biol Chem*, **161**, 621.
— Lilienthal, J L, Proemmel, D D, and Franke, R E (1946) "On the Determination of the Physiologically Effective Pressures of Oxygen and Carbon Dioxide in Alveolar Air" *Amer J Physiol*, **147**, 191
Schmidt, C F., Durrke, P L, and Dripps, R. D (1939) "Part played by Carotid Reflexes in Respiratory Responses of Dogs to Small Charges of CO_2 Tension in Arterial Blood" *Amer. J Physiol*, **128**.
— and Comroe, J H, Jun (1940). "Functions of the Carotid and Aortic bodies" *Phy. Rev*, **20**, 115
Sonne, C. (1934) "Der respiratorische luftaustausch in den lungen" *Zschr. ges Exper. Med*, **94**, 13
West, H F (1920) "Clinical Studies of Respiration" *Arch Int Med.*, **25**, 306.
Whitehead, W K., O'Brien, E J, and Tuttle, W M (1942) "Bronchospirography" *J. Thor Surg*, **11**, 266.
Willson, H G (1922) "The Terminals of the Human Bronchiole." *Amer. J. Anat*, **30**, 267.
Zavod, W A. (1940) "Bronchospirography" *J Thor Surg*, **10**, **1**, 27.

more severe cases there may be some enlargement of the hilar
l accentuation of normal lung markings, most pronounced to-
ases of the lungs, these changes are mainly attributable to
rgement If the inflammation spreads to the bronchioles, a fine
y be produced by atelectasis of lung lobules, these appearances
those of diffuse broncho-pneumonia Areas of benign aspiration
(see page 123) may be seen in occasional cases in which the clinical
at of a simple acute bronchitis

ns

ia —The commonest complications of acute bronchitis are pneumonias.
monly the pneumonias complicating bronchitis are of the non-specific
on " kind (*see* page 123) These vary in severity from benign types, which
detectable only by radiography, to fatal diffuse broncho-pneumonias,
occurring especially in infants and the aged Massive collapse of a
be is an occasional complication, its mechanism is closely related to
the aspiration pneumonias, but a main, rather than a segmental or smaller,
us is concerned Less commonly, bronchitis may pave the way for invasion
lung by one of the organisms causing acute specific pneumonias If dry
complicates bronchitis, it is due to one of these pneumonic complications

erbation of chronic pulmonary disease —Acute bronchitis frequently
exacerbations of the symptoms of chronic diseases of the lung In bronchi-
s, for instance, after an attack of bronchitis, not only are the symptoms
ated, but in the radiographic picture any abnormal shadowings that may be
nt are accentuated, or new abnormal shadows may appear in the affected
(*see* Figs 22–24) In patients with chronic fibrotic pulmonary tuber-
is, acute bronchitis may cause similar changes, both in symptoms and
graphic signs ; the decision whether these increased radiographic signs are
ed secondary to the bronchitis or are due to fresh activity of the tuberculous
se is difficult These non-specific " flares " around chronic pulmonary
ns after acute bronchitis are probably due to localized pneumonic consoli-
ions

Congestive heart failure —In chronic morbus cordis, acute bronchitis may
a factor in determining the onset of congestive heart failure The most clear
ample of this is in cases of chronic cor pulmonale secondary to pulmonary
physema, in which episodes of congestive failure are usually initiated by an
ute bronchitis In rheumatic heart disease with mitral stenosis, intercurrent
onchitis sometimes seems to precipitate congestive failure In hypertensive
rt disease, too, an episode of congestive failure may be preceded by acute
nchitis, although this must be distinguished carefully from acute pulmonary
ma. Unless there is pre-existent heart disease, heart failure does not com-
acute catarrhal bronchitis.

bronchitis —The history of most cases of chronic bronchitis usually
nset recurrent attacks of acute bronchitis The relative importance
e environmental factors—such as severe climatic conditions,
and poor general hygiene—preventing the proper resolution of

ceptions noted below, they show no certain relation to clinical features lthough knowledge of the virus or viruses associated with the common upper espiratory catarrhal infections is scanty, it seems likely that these agents may ave an influence in initiating the common catarrhal bronchitis In the case of influenza, there can be little doubt that a specific virus bronchitis occurs.

Pathology

The changes in the bronchial mucosa in catarrhal bronchitis are probably similar to those in the nasal mucosa in the acute rhinitis of a common cold. In the initial dry stage, there are hyperaemia and some swelling of the mucosa, which blocks the ducts of the mucous glands In the next stage, there is copious secretion from the bronchial glands, and desquamation of the ciliated epithelium More or less inflammatory reaction occurs in the peribronchial tissues, in severe cases accompanied by some inflammatory swelling of the broncho-pulmonary lymphatic glands A purulent stage may follow, the secretions becoming full of polymorph cells The changes, in the average case, are confined to the larger bronchi : in severe cases, especially in infants and in the aged, they may extenc towards the bronchioles This extension almost inevitably gives rise to areas o lobular atelectasis, which become infected, leading to a patchy pneumonia

Clinical features

Symptoms —A typical attack in an adult usually starts with symptoms of a upper-respiratory infection of varying grades of severity—malaise, headache, coryza, sore throat, and sometimes shivery sensations not amounting to an actual rigor Then, after a day or two, a raw feeling behind the sternum, with an irritant dry cough, begins , the temperature is usually raised a few degrees and the pulse rate increased in proportion The voice may become husky After another day, expectoration begins At first, scanty tenacious clear mucoid secretion is produced with difficulty ; later the secretion becomes more profuse, muco-purulent and more easily expectorated Generally the temperature has settled within a week, and the patient's general condition rapidly improves, although some cough and scanty muco-purulent expectoration in the mornings continue for a variable time The severity of the illness depends to a large extent upon the depth to which the bronchial tree is affected With an infection descending no lower than the main bronchi, the patient may remain ambulant ; when it affects the smaller divisions, a more severe illness, often with perceptible dyspnoea, occurs

Signs —The physical signs are entirely auscultatory in simple bronchitis and vary with the depth to which the inflammation extends If the larger tubes only are involved, there may be no abnormal signs or an occasional low-pitched rhonchus When the smaller tubes are affected, medium or high-pitched rhonchi are audible all over the lung fields at first, and later, when secretion becomes freer, bubbling râles may be audible, especially at the bases , the latter must be distinguished from the finer râles associated with consolidation Occasionally rhonchal fremitus may be detected

Radiological appearances

Many mild cases of acute bronchitis give rise to no recognizable radiographic

change In more severe cases there may be some enlargement of the hilar shadows and accentuation of normal lung markings, most pronounced towards the bases of the lungs; these changes are mainly attributable to vascular engorgement If the inflammation spreads to the bronchioles, a fine mottling may be produced by atelectasis of lung lobules, these appearances merge into those of diffuse broncho-pneumonia. Areas of benign aspiration pneumonia (*see* page 123) may be seen in occasional cases in which the clinical picture is that of a simple acute bronchitis

Complications

Pneumonia.—The commonest complications of acute bronchitis are pneumonias Most commonly the pneumonias complicating bronchitis are of the non-specific "aspiration" kind (*see* page 123) These vary in severity from benign types, which may be detectable only by radiography, to fatal diffuse broncho-pneumonias, the latter occurring especially in infants and the aged Massive collapse of a lower lobe is an occasional complication, its mechanism is closely related to that of the aspiration pneumonias, but a main, rather than a segmental or smaller, bronchus is concerned Less commonly, bronchitis may pave the way for invasion of the lung by one of the organisms causing acute specific pneumonias If dry pleurisy complicates bronchitis, it is due to one of these pneumonic complications

Exacerbation of chronic pulmonary disease.—Acute bronchitis frequently causes exacerbations of the symptoms of chronic diseases of the lung In bronchiectasis, for instance, after an attack of bronchitis, not only are the symptoms aggravated, but in the radiographic picture any abnormal shadowings that may be present are accentuated, or new abnormal shadows may appear in the affected areas (*see* Figs 22-24) In patients with chronic fibrotic pulmonary tuberculosis, acute bronchitis may cause similar changes, both in symptoms and radiographic signs; the decision whether these increased radiographic signs are indeed secondary to the bronchitis or are due to fresh activity of the tuberculous disease is difficult These non-specific "flares" around chronic pulmonary lesions after acute bronchitis are probably due to localized pneumonic consolidations

Congestive heart failure.—In chronic morbus cordis, acute bronchitis may be a factor in determining the onset of congestive heart failure The most clear example of this is in cases of chronic cor pulmonale secondary to pulmonary emphysema, in which episodes of congestive failure are usually initiated by an acute bronchitis In rheumatic heart disease with mitral stenosis, intercurrent bronchitis sometimes seems to precipitate congestive failure In hypertensive heart disease, too, an episode of congestive failure may be preceded by acute bronchitis, although this must be distinguished carefully from acute pulmonary oedema Unless there is pre-existent heart disease, heart failure does not complicate acute catarrhal bronchitis

Chronic bronchitis.—The history of most cases of chronic bronchitis usually shows at the onset recurrent attacks of acute bronchitis. The relative importance of unfavourable environmental factors—such as severe climatic conditions, insufficient care, and poor general hygiene—preventing the proper resolution of



FIG 22.—Radiograph of the chest of a woman suffering from bronchiectasis, taken during an episode of acute bronchitis. Note the consolidation in the right lower and right upper zones

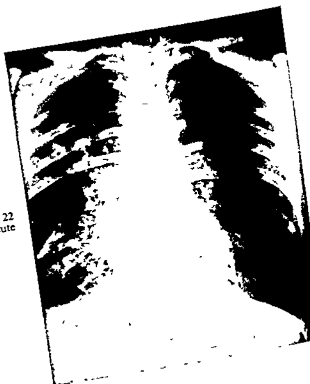


FIG 23.—Same patient as in Fig 22 after recovery from the acute attack



FIG 24—Bronchogram of the same patient as in Fig 22 showing bronchial dilatation in both lower lobes The acute bronchitis in this case was complicated both by consolidation around the dilated bronchi in the right lower lobe, and by aspiration pneumonia in the right upper lobe where the bronchi are of normal calibre

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F INFANTS

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Post-operative bronchitis

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... suffere...
... uric...
exacerbation of the chronic condition. ...
to be complicated by pneumonias, especial...
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Differential diagnosis

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ng mucus by suction,
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develops, the cause of this must be sought in some pre-existent lesion of t
cardiovascular system, and the condition treated according to the findings

Convalescence—An adequate period of convalescence under good conditic is of great importance, especially in young children and the aged, in view of t susceptibility to recrudescences

ACUTE LARYNGO-TRACHEO-BRONCHITIS OF INFANTS

This title has been used to describe a group of cases of severe acute infection of respiratory tract in infants and young children The illness is characterized cli cally by evidence of laryngitis, tracheitis and bronchitis, with obstruction in larynx and trachea which may closely simulate that of diphtheria, and w episodes of severe dyspnoea

Clinical picture

The infant is severely ill, often pale, with obstructed noisy respiration a inspiratory indrawing of the intercostal spaces, the physical signs in the lu are those of a generalized bronchitis, without localizing signs to suggest pneumor By endoscopy, Chevalier Jackson has shown that in these cases characteristica the laryngeal mucosa is deep red, but the main obstruction is due to swelling the subglottic tissues, the connective tissue in this region being lax in childr (Jackson and Jackson, 1950) Small patches of secretion are seen in the muco but there is neither ulceration nor membrane-formation The tracheal a bronchial mucosa is acutely inflamed and swollen When the exudate becor purulent, it tends to dry into crusts which, together with the swollen muco obstruct the lumina of bronchi, giving rise to atelectasis of variable portions of lung, which may simulate pneumonic patches, or may actually become pneumo if they become infected Bacteriological findings are inconstant, althou haemolytic streptococci are sometimes found in association with this conditic although no specific virus has been isolated, some authorities favour a vi aetiology

Diagnosis

The importance of the condition rests upon its differential diagnosis fr laryngeal diphtheria, and upon certain therapeutic indications For diagno laryngoscopy may be necessary, although, in any doubtful case, diphthe antitoxin should be given

Treatment

In treatment, the importance of an adequately humid atmosphere must emphasized The newer antibiotics, notably chloramphenicol, may be effecti and should be given in a dosage appropriate to the child's age Danger obstruction of the air-passages by the sticky secretions and by subglottic swell may necessitate tracheotomy, and when indicated this should not be delay In less urgent cases, bronchoscopy and removal of obstructing mucus by sucti or of crusts of dried secretion by forceps, may be sufficient to maintain air-way.

distinct variety of acute bronchitis, characterized by the expectoration of casts or of parts of the bronchial tree Probably it is best to regard this phenomenon as one which may occur in the course of several types of bronchitis, rather than as characterizing a distinct variety

Aetiology

The majority of the reported cases have occurred in the course of chronic affections of the bronchi, patients with chronic bronchitis having occasional acute attacks associated with the formation and expectoration of a cast Others have been reported in association with heart disease, with pulmonary tuberculosis, with asthma or with pulmonary oedema after thoracentesis A few have seemed to be a distinct variety of acute bronchitis, and acute cases have also been reported in association with typhoid fever, scarlet fever and measles

The formation of the casts may be merely an abnormal reaction to the factors which usually produce a catarrhal bronchitis The name, fibrinous, is misleading, since the casts consist mainly of mucin, with only a little fibrin They are generally expectorated as rolled-up masses, and their true conformation can be observed only if they are floated out in water Possibly, if sputa were investigated in this way more frequently, small bronchial casts might be found more often in simple bronchitis

Clinical picture and course

In well-marked acute cases, the onset is similar to that of a severe catarrhal bronchitis , after a few days, dyspnoea and cyanosis develop, and there is evidence of partial obstruction to the air-way, in the form of indrawing of intercostal spaces and action of the accessory muscles of respiration Collapse of a lobe or lobes of the lung, with its resultant physical signs, may occur After a time, generally about a week from the first onset of the bronchitis, the cast is expectorated, with immediate relief of symptoms , but in a number of the reported cases there has been repeated re-formation of the cast There is said to be some risk of impaction of the cast in the larynx, but apart from this the immediate prognosis is not unfavourable

Treatment

Treatment is as for severe catarrhal bronchitis Potassium iodide is usually recommended to hasten the separation of the cast and to discourage its re-formation Chevalier Jackson mentions two cases in which symptoms were relieved by bronchoscopic removal of the cast

ACUTE BRONCHITIS IN SPECIFIC INFECTIONS

Influenza —In influenza of moderate severity, clinical evidence of bronchitis is always present, and in fatal cases severe tracheitis and bronchitis are constant findings The inter-relation between the bronchitic and pneumonic changes in [illegible]

[illegible] may present, as one of their principal [illegible] primarily due to their specific causative agents. The initial bronchitis of measles, preceded or accompanied by coryza

ACUTE [illegible]RATIVE TRACHEO-BRONCHITIS

A more sever form [illegible] .hitis, characterized by the early appearance of a purulent stage, b[illegible] iemia, and a high death-rate, occurs sporadically In 1917, a disease [illegible] it appeared in epidemic form among British troops both in England [illegible] rance It was generally described under the title of purulent bronc[illegible] uncertain whether this disease is aetiologically specific, or is merel[illegible] orm of simple catarrhal bronchitis, occurring in an individual or [illegible] ny whose resistance is lowered by exhaustion and bad hygiene [illegible] whom certain bacteria or groups of bacteria have becom[illegible] nt flora.

[illegible] 'le to distinguish a case of purulent bronchitis from [illegible] especially as there is quite frequently a preceding [illegible] days, there appear dyspnoea and cyanosis, with [illegible] .nkly purulent sputum, often blood-stained at first, [illegible] to 103–104° F. In some cases, the patient lapses [illegible] lly torpid state with increasing tachypnoea and cyanosis, [illegible] At autopsy, universal gross purulent bronchitis is found, [illegible] nchi by pus, and with areas of collapse, but often very [illegible] umonia In others, the course is more prolonged; [illegible] e maintained for 3–6 weeks, with profuse sweating, [illegible] purulent expectoration. Most of the patients with such prolonged ill[illegible] er but the average mortality may be high In a very large proportion of th[illegible] ases in 1917, culture of the sputum showed Pfeiffer's bacillus, often [illegible] with a pneumococcus.

Diagnosis

The diagnosis may be difficult in a sporadic case A general aspect suggesting pneumococcal pneumonia, combined with physical signs of bronchitis without consolidation, and with the expectoration of copious pus, is very suggestive A radiograph may show diffuse mottling, due either to secretion in the bronchi or to scattered lobular atelectasis; the determination of the stage at which fine broncho-pneumonia is present is somewhat arbitrary. In the more prolonged cases, acute broncho-pneumonic pulmonary tuberculosis may be simulated by the general condition, but the absence of tubercle bacilli from the purulent sputum suffices to eliminate this possibility.

Treatment

In addition to similar measures as for severe catarrhal bronchitis, oxygen should be given continuously by an efficient method Penicillin or some other suitable antibiotic should be given from the onset. A suitable sulphonamide should be given if the bacteriology of the sputum suggests that it might be useful, and if response to penicillin has been unsatisfactory.

ACUTE FIBRINOUS OR PLASTIC BRONCHITIS

Under the title, acute fibrinous bronchitis, the older text-books described a

CHAPTER 4

CHRONIC BRONCHITIS

J. G. SCADDING

IN TEMPERATE and changeable climates such as that of Great Britain, the malady generally described under the title chronic bronchitis is one of the commonest of chronic illnesses The diagnosis is essentially a clinical one, and although the clinical picture is easily recognizable, many factors may play a part in its causation. and the pathological changes are by no means uniform The disease may arise in previously healthy persons, or it may be associated with asthma or other allergic disorders or with chronic nasal infections ; and it may complicate chronic cardiovascular or renal disease

CLINICAL PICTURE

The principal symptoms of chronic bronchitis are persistent cough, productive of a variable amount of expectoration, which may be either mucoid or mucopurulent, and progressive dyspnoea on exertion In those cases of chronic bronchitis which arise insidiously, the most frequent age of onset is at or after middle-age The common history is that the symptoms start in the winter after a cold which is followed by a cough and expectoration In succeeding winters the number of acute attacks of this sort and the duration of the cough after each attack progressively increase. This first phase of recurrent bronchitis—with symptoms confined to the winter months and clearing up entirely in the summer—gradually gives place as the years go on to a second phase of constant cough, expectoration and dyspnoea on exertion, with winter exacerbations, usually associated with intercurrent respiratory infections The sputum is purulent or muco-purulent during and immediately after an exacerbation, but usually becomes less purulent in the intervals, and during the summer

The symptoms may begin much earlier in life Those beginning in childhood are commonly associated with asthma In a few of these cases the symptoms may diminish in severity or even clear up completely at puberty In others, however, the number and severity of attacks of winter bronchitis steadily increase, and eventually symptoms become continuous throughout the year

Sooner or later [illegible]

almost invariably develops, so that the terminal picture in all cases is that of bronchitis, asthma and emphysema Intercurrent infection often gives rise to *pneumonic episodes of varying severity, mostly of the aspiration type* A varying degree of dilatation of the basal bronchi often develops, presumably from gradual weakening of their walls, and sometimes more localized bronchiectatic changes appear as a resul[illegible] he episodes of aspiration pneumonia or infected atelectasis.

characterized by slowly in[illegible]ing dyspnoea and cyanosis, together with signs of bronchitis, but with[illegible] e[illegible]ence of consolidation of the lung. No constant bacteriological findings h[illegible] been recorded. Radiologically, there is diffuse mottling, coarser than th[illegible] miliary tuberculosis. Proof of the diagnosis of such a rare condition, the clini[illegible]l picture of which is relatively ill-defined, depends upon findings at autops[illegible] These consist of desquamative inflammation of the bronchioles with muc[illegible] fibrous tissue around them, giving rise to more or less discrete nodule[illegible]

Mustard gas

In poiso[illegible] gas, on the other hand, the principal early effects on th[illegible] are severe laryngitis, tracheitis and bronchitis, the sy[illegible] [illegible]elay of 2–48 hours from the exposure. Most of the [illegible] [illegible]lary pneumonia At autopsy, the bronchial tree, right d[illegible] [illegible]les, shows an intense necrotizing inflammation The n[illegible] [illegible] [illegible]brin and pus cells, may form a slough which separates in p[illegible] leaving supe[illegible]cial ulcers. The necrotizing bronchiolitis and the accumulation [illegible] [illegible]ed secretions give rise to a secondary patchy septic pneumon[illegible] [illegible] [illegible]lso produces, of course, serious effects on the skin and eye

[illegible]

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BIBLIOGRAPHY

Acute laryngo-tracheo[illegible] of infants

Jackson, C. and J[illegible] [illegible]) *Broncho-oesophagology*, p. 121. Philadelphia and London Saunders

Moncrieff, A., and W[illegible] V (1949) "Acute Laryngotracheobronchitis treated with Chloromycetin" *Lancet* [illegible], 748

Purulent tracheo-bronchitis

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Hammond, J A B, Rolland W, and Shore, T. H G (1917). "Purulent Bronchitis" *Lancet* 2, 41

Fibrinous bronchitis

Bettmann, M (1902) "Report of a Case of Fibrinous Bronchitis with a Review of all the Cases in the Literature" *Amer. J med Sci*, **123**, 304.

Walker, I C. (1920) "Fibrinous Bronchitis" *Amer. J med Sci*, 159, 825.

Bronchitis due to dust inhalation

Perry, K M A. (1947) "Diseases of the Lung resulting from Occupational Dusts other than Silica" *Thorax*, 2, 91

Teleky, L (1938) "*Pneumoconiosis*" In *Occupation and Health (I L O)*, Supplement, January

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Moncrieff A [illegible] D V (1949). "Acute Laryngotracheobronchitis treated with Chloromycetin" *Lancet* 2, 748

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Sooner or later in nearly all cases of chronic bronchitis emphysematous changes develop in the lungs, and the course and prognosis are then those of emphysema In addition, even in cases not primarily asthmatic, more or less bronchial spasm almost invariably develops, so that the terminal picture in all cases is that of bronchitis, asthma and emphysema Intercurrent infection often gives rise to pneumonic episodes of varying severity, mostly of the aspiration type A varying degree of dilatation of the basal bronchi often develops, presumably from gradual weakening of their walls, and sometimes more localized bronchiectatic changes appear as a result of the episodes of aspiration pneumonia or infected atelectasis

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BIBLIOGRAPHY

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Fibrinous bronchitis

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appear as a result of the episodes of aspiration pneumonia or infected atelectasis

AETIOLOGY

lthough certain unfavourable environmental factors seem to predispose to the evelopment of chronic bronchitis, the most important aetiological factor in nost cases is constitutional A family history of similar affections is frequently ound, sometimes running through several generations The relation of some cases asthma, which of course is often familial, has already been noted The chief nvironmental factors predisposing to chronic bronchitis are poor housing, xposure to cold and damp at home or at work, and exposure at work to violent hanges of temperature and to various dusts Excessive smoking is a factor some cases, and presumably acts by long-continued chemical irritation of the ronchial mucosa

Recurrent respiratory infections develop and persist, presumably because of the nderlying abnormality of the respiratory mucosa , they tend to produce further amage to the mucosa, and thus set up a vicious circle rendering the mucosa ill more susceptible to further infections

PATHOLOGY

t necropsy, the pathological picture of chronic bronchitis is usually complicated by rminal pneumonic changes, nearly always by emphysema, and often by more r less bronchial dilatation The latter most often affects the basal bronchi, e walls of which are thin, atrophic and stretched. Sometimes bronchiectatic hanges may be found localized to other broncho-pulmonary segments than the asal ones Elsewhere the mucous membrane of the bronchi may be either vollen and hypertrophic or thin and atrophic The bronchi contain muco-pus pus Histologically the epithelium loses its normal ciliated columnar form and ecomes cubical or flat and in places desquamates There is a variable amount cellular infiltration and fibrosis of the bronchial wall, and in severe cases fibrous ssue may replace the bronchial glands and muscle tissue In most cases there is vidence of right ventricular hypertrophy, and in those in which the secondary nphysema has been severe the changes associated with right ventricular failure ay be found

PHYSICAL SIGNS

hronic bronchitis characteristically gives rise to persistent rhonchi widely attered over the lungs, and these constitute the only distinctive physical signs hey are variable in pitch , if, as often happens, there is an appreciable degree bronchial spasm, they are more prolonged and higher in pitch during expiration. fter a bout of coughing the rhonchi often diminish in intensity or clear up, [illegible]

quiescent phase, they suggest basal bronchiectasis In uncomplicated chronic itis the fingers are not clubbed

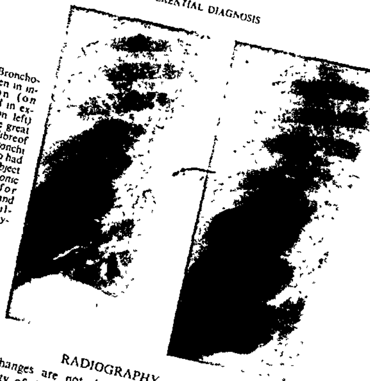


FIG 25.—Bronchogram taken in inspiration (on right), and in expiration (on left) to show the great change in calibre of the basal bronchi in a man who had been the subject of severe chronic bronchitis for many years, and had also pulmonary emphysema

RADIOGRAPHY

The radiographic changes are not distinctive There may be some general increase in the density of the vascular markings of the lung as compared with those of a normal chest taken with the same technique The changes associated with emphysema may be evident Bronchography in severe cases will often show some irregularity in the calibre of the bronchi, even if this does not amount to dilatation Sometimes in such cases bronchograms taken in inspiration and expiration will demonstrate the flaccid state of the basal bronchi, by showing them to be dilated in inspiration and to collapse in expiration (Fig 25).

DIFFERENTIAL DIAGNOSIS

The diagnosis of chronic bronchitis should not be accepted without careful exclusion of other conditions which may cause similar symptoms In children asthma may present first in the form of prolonged attacks which suggest recurrent sub-acute bronchitis, and indeed the differentiation between bronchitis and asthma may be very difficult. Many asthmatics are liable to recurrent prolonged attacks with bronchitic symptoms and may eventually develop chronic inflammatory changes in the bronchial mucosa, and conversely many cases which start with the typical picture of chronic bronchitis without obvious bronchial spasm develop bronchial spasm later with asthmatic symptoms In children also it is especially important to consider whether symptoms suggestive of a

CHAPTER 5

THE PNEUMONIAS

J G. SCADDING

CLASSIFICATION AND NOMENCLATURE

Definition

ETYMOLOGICALLY the word pneumonia, like its synonym, pneumonitis, means "inflammation of the lung"; but by convention its application is usually confined to those forms of pulmonary inflammation which are characterized predominantly by exudation into the alveoli. This convention excludes from the pneumonic group those forms of pulmonary inflammation the chief effects of which are fibrosis, suppuration or necrosis, even though these changes may be present incidentally in some pneumonias Thus the fibrotic stages of pulmonary tuberculosis are excluded, even though, on the one hand, an active stage of the same disease with widespread alveolar exudation may legitimately be termed tuberculous pneumonia, and, on the other hand, a pneumococcal pneumonia may very occasionally end in organization leading to fibrosis. It is clear that, even with this conventional limitation, a large variety of morbid conditions are included under the heading, pneumonia

Classification and nomenclature

The nomenclature of the pneumonias is at present in a very confused state The older system was based almost exclusively upon anatomical features, the principal distinction being between lobar pneumonias and lobular pneumonias or broncho-pneumonias The development of specific methods of therapy,

can be either lobar or lobular in distribution An important proportion of pneumonias can in fact be classified conveniently on this basis of specific causative agents, they are here called "acute specific pneumonias" Classification of all pneumonias on such a basis, however, is not, in practice, possible. This is due not only to incomplete knowledge of aetiological agents but also to certain anatomo-physiological peculiarities of the lungs There is a large group of pneumonias which are primarily due to a breakdown of the normal defences of the respiratory tract, allowing organisms which are not specifically pathogenic to gain access to the lung. This group cannot conveniently be classified and named according to causative organisms; pneumonias of this group are here called "aspiration pneumonias". The reasons for applying this term to them are discussed below (page 62). A classification of pneumonias based on these considerations is given in Table I

TABLE I

CLASSIFICATION OF PNEUMONIAS

(1) *Acute specific pneumonias*

Causal factors	Remarks
Bacterial	
Str pneumoniae (pneumococcus)	
Str haemolyticus	
Staph aureus	
Friedländer's bacillus	
Myco tuberculosis	
B influenzae	Rare, apart from association with influenza virus
Anthrax bacillus	Wool-sorter's disease
Past pestis	Pneumonic plague
Past tularensis	
Associated with virus diseases	
Influenza	The pneumonias associated with these two virus diseases are caused by the joint effects of the virus and various bacteria
Measles	
Viral	
Psittacosis-ornithosis group	
Unidentified pneumonotropic viruses	
Viruses of recognized acute specific diseases	
Rickettsial	
R burneti	Q fever
Fungal	
[illegible]	[illegible]
Plasmodia	
[illegible]	Malignant tertian malaria
Chemical	
Lung-irritant gases	
Lipoids	
Allergic	Loeffler's syndrome, eosinophilic infiltrations of the lung, periarteritis nodosa

(2) *Aspiration pneumonias*

Type		
Diffuse	Synonyms	Broncho-pneumonia
	Varieties	Post-operative, hypostatic terminal, post-bronchitis deglutition, inhalation
Localized	Synonyms	Infected segmental atelectasis; pneumonitis
Suppurative	Synonyms	Suppurative pneumonitis, necro-suppurative broncho-pneumonia, lung abscess (most types)

Acute specific pneumonias

The acute specific pneumonias, classifiable according to their specific causat agents, can be divided into several groups, of which the first four are of great importance.

Pneumonias due to bacteria are probably the most numerous; they res from infection of the lung by specifically invasive bacteria. Pneumococ pneumonia is the typical example of this group. Characteristically, they have well defined course and produce well marked immunity reactions in the blo and tissues of the patient; chemotherapeutic and antibiotic substances effecti against the causative organisms give good results in treatment.

A special category is necessary for the pneumonias associated with influen and with measles. Although in many animals the normal pattern of seve influenzal infection includes a pure virus pneumonia, without additional infecti by bacteria, in man the pneumonias associated with influenza are due to t combined action on the lungs of the influenza virus and of a variety of bacter of, at least, potential independent pathogenicity. In measles, it is certain th bacteria are similarly responsible, at least in part, for the pneumonic complication

The pneumonias due to pure virus infections of the lung are a difficult grou since the detection of the causative virus is so much more difficult than is that the causative bacteria in bacterial pneumonias. Pneumonias due to viruses the psittacosis-ornithosis group are at present the only ones due to a named ar generally identifiable virus. There is no doubt, however, that a large and importa group of pneumonias in man are due to either pneumonotropic viruses, whic have been less completely, or in some instances not at all, identified in th laboratory. These are classified as "pneumonias presumed due to unidentifie pneumonotropic viruses". The problem presented by these cases is complicate by the fact that common colds, as well as similar epidemic upper-respirator infections of presumed virus origin, have an important effect in predisposing t bacterial pneumonias and in initiating certain pneumonias of the aspiratio group, but there is no evidence that in these instances the viruses are concerne in the actual lung lesion.

The most important member of the rickettsial pneumonia group is the pneumoni caused by the virus of Q fever, *Rickettsia burneti*. This has been shown to occu in widely scattered localities all over the world.

Aspiration pneumonias

Aetiological factors

There is a large group of pneumonias, which occur in the course of various acute and chronic catarrhal infections of the respiratory tract, in conditions of debility from chronic systemic disease or old age, after operations, or during coma from any cause, in which the bacterial flora is mixed and may contain no specially invasive organisms, and in which there is no evidence that any specific virus is concerned. Some of these pneumonias are diffusely lobular in distribution, most often at the bases though occasionally in other parts of the lungs; but sometimes the lesions may be confined to one or a few broncho-pulmonary segments. They are usually termed broncho-pneumonias, although this term

has been used also to denote those forms of acute specific pneumonia which appear in a lobular distribution, descriptive terms such as "hypostatic", "post-operative", "terminal", and "secondary" are added to denote varieties within the group. Reimann (1938) has called this group "secondary broncho-pneumonias caused by mixed infection". Unfortunately, "secondary broncho-pneumonia" has also been used to describe the pneumonias which occur in association with virus diseases, such as measles and influenza; these are aetiologically distinct, and it is undesirable to use the same term for aetiologically distinct diseases.

In distribution, in clinical and radiographic features, and in morbid anatomy, these pneumonias have much in common with those which are obviously caused by inhalation of foreign material, such as may occur after vomiting during anaesthesia, or in relation with laryngeal palsy, with new growths in the larynx and pharynx and so forth; these relatively rare varieties will here be termed "inhalation pneumonias". It seems likely that, just as the inhalation pneumonias are due to the aspiration of exogenous matter, so the patchy "secondary" pneumonias associated with mixed bacterial flora are due to aspiration of endogenous matter, mainly the excessive secretions of the respiratory tract itself. It thus seems reasonable to describe both groups by the term, aspiration pneumonia, which is taken to include all those pneumonias in which the production of the pneumonic reaction does not depend primarily upon the presence of especially invasive bacteria, but upon unfavourable factors interfering with the normal mechanics of the broncho-pulmonary system, which enable either endogenous secretions or, more rarely, exogenous matter to gain access to the deeper parts of the intrapulmonary air passages. The common factor in aspiration pneumonias is that they are due to a breakdown in the normal mechanical defences of the respiratory tract. In the alveoli, naked capillaries are exposed to the air, since the alveolar epithelium, the existence of which in adult life is denied by some observers, is admitted to be discontinuous, even by those who believe that it exists in the normal adult lung. These capillaries may be regarded as the equivalent of an open wound, defended against contamination by air-borne matter and by endogenous secretions from within the respiratory tract by the elaborate defence mechanisms which exist in the nose, the larynx, and the tracheo-bronchial tree. These consist in the warming, humidifying and filtering function of the nose, the cough reflex, the ciliary mechanism in the tracheo-bronchial tree and the abundant lymphoid tissue which exists throughout the broncho-pulmonary system. If this elaborate defence breaks down, bacteria or even sterile irritant substances may gain access to the alveoli, and there give rise to inflammatory reactions which do not depend for their inception upon any specific pathogenic properties of the bacteria themselves. Experimentally, it has been shown that various organic materials, introduced into the bronchi of animals, even if bacteriologically sterile, can produce a transient pulmonary consolidation, distinguishable from atelectasis by the presence of an inflammatory exudate in the alveoli. Thus Kline and Meltzer, in 1915, described, in dogs which had received intrabronchial injections of various unorganized substances, "lesions which macroscopically could not be distinguished from those produced by insufflation of pneumococci." Gunn and Nungester (1936) described lesions produced in rats by the intratracheal

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The pneumonias due to pure virus infections of the lung are a difficult group, since the detection of the causative virus is so much more difficult than is that of the causative bacteria in bacterial pneumonias. Pneumonias due to viruses of the psittacosis-ornithosis group are at present the only ones due to a named and generally identifiable virus There is no doubt, however, that a large and important group of pneumonias in man are due to either pneumonotropic viruses, which have been less completely, or in some instances not at all, identified in the laboratory These are classified as " pneumonias presumed due to unidentified pneumonotropic viruses " The problem presented by these cases is complicated by the fact that common colds, as well as similar epidemic upper-respiratory infections of presumed virus origin, have an important effect in predisposing to bacterial pneumonias and in initiating certain pneumonias of the aspiration group ; but there is no evidence that in these instances the viruses are concerned in the actual lung lesion

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aspirated Weakness of the muscles of respiration, caused by debilitating illness, prolonged decubitus, old age, and so forth, reduces the effectiveness of cough in emptying the bronchi of secretions Depression of the sensitivity of the cough reflex during anaesthesia, as a result of the administration of narcotics, or even during deep sleep, may allow secretions to collect undisturbed

The view advanced here is that, in this group of pneumonias, infection is non-specific and of less aetiological importance than are the various factors, mainly mechanical, outlined above. The term, aspiration pneumonia, although not an ideal one, thus accords with the principle of aetiological nomenclature, since it is expressive of the chief factors in the pathogenesis of these pneumonias Its use avoids the confusion, noted above, which surrounds the term, broncho-pneumonia "Aspiration pneumonia" also has the advantage that it draws attention to the important relation which exists between this group of pneumonias and some of the commoner varieties of acute pulmonary suppuration

Incidence of various aetiological types of pneumonia

The incidence of pneumonia due to various aetiological agents differs widely from place to place and from time to time It appears that the pneumococcus continues to be the most frequent cause of pneumonia, although hospital statistics obtained since the introduction of specific chemotherapeutic and antibiotic treatment are difficult to interpret This is not only because fewer cases are admitted to hospital, but also because the administration of specific therapeutic agents before admission may interfere with aetiological investigation There is a general impression that non-pneumococcal pneumonias—and in particular pneumonias presumably due to unidentified pneumonotropic viruses—are becoming more frequent, but again it is difficult to say whether or not this impression may be due to increase in knowledge of and interest in such conditions For example, it was not generally known until about 1945 that the rickettsia of Q fever might be an important cause of obscure febrile illness having a pneumonia as one of its principal features, since then the occurrence of such illnesses has been reported in more and more parts of the world Similarly, the knowledge that human infections by viruses of the psittacosis-ornithosis group may be derived from other sources than birds of the parrot family has led to the detection of such infections, apparently derived from a variety of vectors, in several parts of the world There can be little doubt that infections of these two sorts have occurred in the past, but have gone undiagnosed

Epidemics of such respiratory infections as influenza give rise to variations not only in the total incidence of pneumonias, but also in the differential incidence of various types of pneumonia The situation is complicated by two facts (1) that some pneumonias, notably those associated with influenza, are of mixed aetiology, (2) that the epidemic febrile catarrhs which mimic influenza so closely may not only themselves be due to the combined action of more than one agent, but may give rise to pneumonias of similarly mixed aetiology

These considerations show that figures of the incidence of various aetiological types of pneumonia will be applicable only to a particular population at a particular time, and very few complete aetiological investigations of unselected series of pneumonias have been made Humphrey, Joules and van der Walt (1948)

injection of mucin alone, consisting in pneumonic reactions of varying extent, usually poor in fibrin, which might persist as long as 3 days. The probable mechanism by which these pneumonic reactions are caused is initially identical with that of atelectasis. Small bronchi or bronchioles become blocked with the mucus or other material; the air beyond the block is absorbed into the blood stream, and thus the obstructing material tends to be drawn further down towards the alveoli. If the material is neither irritating nor infected, a pure atelectasis of the related segment of the lung occurs; if it is irritant, either from its chemical nature or as a result of any sort of bacterial contamination, an inflammatory reaction is set up in the bronchioles and alveoli, giving rise to a pneumonia.

Clinical effects

Clinically, a lobular pneumonia of varying extent may be produced by a mechanism of this sort in a patient whose respiratory-tract defences have been damaged by systemic or local disease. Bronchitis, of all sorts, is an especially important precedent condition; the production of excessive secretions, interference with the ciliary mechanism and narrowing of the lumen of the smaller bronchi and bronchioles by inflammatory swelling of their mucosa are conditions especially favourable to the aspiration mechanism. The pneumonia may be extensive enough to contribute to a fatal outcome in a patient enfeebled by old age or disease, although none of the organisms recognized as having invasive power in the lungs is present in the sputum, or even in the lungs at necropsy. On the other hand, the aspiration mechanism is probably responsible for the mild localized pneumonias which radiography has shown to be a not infrequent complication of the common catarrhal infections of the respiratory tract, and which are described below under the title of "localized aspiration pneumonia". There is thus a wide variation in the extent of the lesions, as well as in the severity of the symptoms produced by pneumonias of the aspiration type. Furthermore, it is impossible to draw a hard-and-fast line between this group and some of the pneumonias considered to be acute specific infections; cases having some of the characteristics of both groups may occur, as when a pneumonia is initiated by the aspiration mechanism, but the secretions happen to contain a few pneumococci or other independently pathogenic organisms. In such a case, the greater the pathogenicity of the organism present for the individual patient, the more the clinical picture is likely to resemble that of the acute specific pneumonia caused by that organism. Thus, although the inception of aspiration pneumonias is not dependent upon the presence of especially pathogenic organisms, the course is influenced by variations in the bacterial flora.

The determining factor in the initiation of aspiration pneumonias is interference with the normal defence mechanisms of the lower respiratory tract. There are several ways in which the defences may be impaired. The ciliary mechanism of the bronchi, which normally keeps a thin sheet of mucus continually moving upwards towards the larynx, may be affected by inflammatory processes ranging from the common cold to chronic bronchitis; these catarrhal conditions of the upper or lower respiratory tracts also provide excessive secretions which may be

Method of description adopted in this chapter

Although typical cases of the various aetiological varieties of pneumonia may present clinical pictures sufficiently distinctive to suggest a specific diagnosis, proof of this rests upon laboratory studies, which will not be available at the time when the practical problem of treatment must be met, in many cases it is impossible even to make a reasonable guess at the specific diagnosis on clinical grounds alone For this reason, in the following description of the pneumonias, the practical problem of treatment is considered separately The individual descriptions of the specific pneumonias include only brief references to important peculiarities of each variety in the matter of sensitivity to sulphonamides and antibiotic agents The practical problem of the treatment of the pneumonias in general is discussed at the end of the chapter.

PNEUMOCOCCAL PNEUMONIA

The acute specific disease caused by infection of the lung by organisms of the pneumococcus group is by far the commonest type of acute specific pneumonia Its typical form presents the classical picture of lobar or fibrinous pneumonia

The pneumococcus

The relation of the organism now called the pneumococcus, or *Streptococcus* (or *Diplococcus*) *pneumoniae*, to pneumonia in man was first established by Frankel in 1886, though the organism had been described by other observers some years previously Pneumococci are Gram-positive, encapsulated, lance-shaped cocci, usually seen in pairs in tissues or secretions, but with some tendency to form short chains in culture They are classed bacteriologically with the streptococci, from the rest of which they can be distinguished by their bile-solubility

Typing of pneumococci

Examined by cultural or staining methods, pneumococci form a homogeneous group, with the exception of type III of the current classification This strain has a thicker capsule, forms moist mucoid colonies, has a greater tendency to occur in short chains, and is more virulent than the other strains, these it is possible to classify only by serological methods

In 1909 Neufeld and Händel prepared a potent monovalent serum against a strain which they called "I", and which is the type I of later classifications, they found that this serum was both protective against infections with the homologous strain, and caused specific agglutination of this strain, but was ineffective in both respects against other strains In 1913, Dochez and Gillespie, in the United States of America, divided pneumococci into four groups their type I was identical with Neufeld's, type II was another strain, distinguishable by specific serological methods, type III was the *Streptococcus mucosus*, and group IV a heterogeneous collection of all other strains At the same time, Lister in South Africa evolved another classification, his types being denoted by letters of the alphabet, some of Lister's types were not included in the American list.

The task of extending Dochez and Gillespie's classification was tackled by many

found that, of 351 cases of pneumonia observed in North-West London between 1942 and 1944, 298 could be attributed with some assurance to bacterial infections, whereas 53 could not be attributed to specific bacterial infection. Table II

TABLE II

INCIDENCE OF PNEUMOCOCCAL AND OTHER PNEUMONIAS IN LONDON, 1942–44*

Infection	Number	Percentage
Pneumococcal	278	79 2
Haemolytic streptococcal	9	2 6
Staphylococcal	7	2 0
Friedlander's bacillus	2	0 6
Other bacteria	2	0 6
Not attributable to specific bacterial infection	53	15·1
Total	351	—

* *After Humphrey, Joules and van der Walt (1948).*

shows the bacteria which they considered responsible for their 298 bacterial cases; it will be noted that the pneumococcal was by far the most frequent. In spite of these authors' fairly complete laboratory investigations, they were able to assign a probable named virus aetiology to only 3 of their 53 cases not attributable to specific bacterial infection; these appeared to be due to viruses *of the psittacosis-ornithosis group*

The above figures may be compared with those in Table III, which show the incidence of pneumococcal and non-pneumococcal pneumonias in the series of Bullowa and Gleich (1938) in New York from 1928 to 1935. The percentages of pneumonias due to specific bacterial agents are very similar in the two series; it is probable that the group labelled "non-pneumococcal" in the figures of Bullowa and Gleich includes cases which would be included in the London series *under the heading "not attributable to specific bacterial infection"*, as well as the small number attributed to specific bacteria

TABLE III

INCIDENCE OF PNEUMOCOCCAL AND NON-PNEUMOCOCCAL PNEUMONIAS IN NEW YORK (1928–1935)*

Infection	Infants 0–2 years		Children 2–12 years		Adults above 12 years		Total, all ages	
	No of cases	*% of** cases*	*No of cases*	*% of cases*	*No. of cases*	*% of cases*	*No. of cases*	*% of cases*
Pneumococcal	381	56 2	371	56 6	3065	85 8	3817	77 8
Non-pneumococcal	297	43 8	285	43 4	508	14 2	1090	22 2
Haemolytic streptococcus	19	2 8	31	4 9	76	2 1	126	3 3
Staphylococcus	17	2 5	16	2 4	26	0 7	59	1·2
Friedländer's bacillus	0	—	0	—	36	1 0	36	0 7
Total	678	—	656	—	3573	—	4907	—

*After Bullowa and Gleich (1938).

** The percentages have been calculated from the figures given in the original paper.

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The relation of the organism now called the pneumococcus, or *Streptococcus* (or *Diplococcus*) *pneumoniae*, to pneumonia in man was first established by Fränkel in 1886, though the organism had been described by other observers some years previously Pneumococci are Gram-positive, encapsulated, lance-shaped cocci, usually seen in pairs in tissues or secretions, but with some tendency to form short chains in culture They are classed bacteriologically with the streptococci, from the rest of which they can be distinguished by their bile-solubility

Typing of pneumococci

Examined by cultural or staining methods, pneumococci form a homogeneous group, with the exception of type III of the current classification This strain has a thicker capsule, forms moist mucoid colonies, has a greater tendency to occur in short chains, and is more virulent than the other strains, these it is possible to classify only by serological methods

In 1909 Neufeld and Handel prepared a potent monovalent serum against a strain which they called "I", and which is the type I of later classifications; they found that this serum was both protective against infections with the

type II was another strain, distinguishable
e III was the *Streptococcus mucosus*, and
of all other strains. At the same time, Lister in South Africa evolved another classification, his types being denoted by letters of the alphabet, some of Lister's types were not included in the American list

The task of extending Dochez and Gillespie's classification was tackled by many

workers , the classification now generally adopted was established by Cooper and her associates who recognized 29 new types, making 32 in all (Cooper, Edwards and Rosenstein, 1929 ; Cooper and her colleagues, 1929). Of the new types, V and VI had previously been included in Dochez and Gillespie's type II, and VIII had been described as an atypical type III, while the rest formed their heterogeneous group IV It now seems probable that of Cooper's original 32 types, two pairs, types XV and XXX, and types VI and XXVI, are identical, leaving 30 specific types The number of pneumococci isolated in the United States which remain outside this classification is small ; but in some other localities a larger number of strains not belonging to any of these types have been reported, and it is probable, therefore, that other types will eventually be added to the list The type-specificity of pneumococci is associated with specific soluble substances, which are present in the capsules of the organisms. These substances are complex carbohydrates, each type having a capsular carbohydrate of constant composition When existing in unfavourable environment, or on assuming the " R " form in culture, the pneumococcus loses the capsular carbohydrate. The presence of the capsular carbohydrate is closely related to the virulence of the organism

Pneumococci are found intermittently or continuously in the nasopharyngeal flora of a large number of persons, even in the absence of disease. The larg majority of the pneumococci thus found belong to the higher types ; wherea types I, II and III, which are the commonest types found in pneumonias, ar which cause the most severe pneumonias, are relatively rarely found in the uppe respiratory tracts of normal persons Gundel (1932) in Heidelberg made 1,5

TABLE IV

INCIDENCE OF PNEUMOCOCCAL TYPES IN PNEUMONIA IN TWO LARGE AMERICAN SERIES

	Tilghman and Finland (1937) (in Boston)		Bullowa and Wilcox (1937) (in New Yor		
			Adults		Children
Lower types	No of cases	Per cent	No of cases	Per cent	No of cases
I	457	28.9	725	23.6	120
II	185	11.6	256	8.4	12
III	262	16.5	297	9.7	35
Others	682	43.0	1788	58.3	582
Total	1,586	100.0	3,066	100.0	749
More commonly found higher types	No of cases	Per cent	No of cases	Per cent	No of cases
IV	36	2.3	179	5.8	38
V	100	6.3	230	7.3	40
VI	—	—	—	—	80
VII	87	5.5	194	6.3	18
VIII	139	8.8	225	7.3	19
XIV	33	2.1	87	2.8	131
XIX	—	—	—	—	39

Types with less than 5% incidence in all three series omitted

examinations of the saliva of 108 children over a period of 10 months, and found pneumococci in 908 (or 57·5 per cent) of the examinations Of the pneumococci

and occasionally more than one type appeared together Pneumococci were detected at some time during the investigation in all but 3 of the children The incidence of pneumococcal types in pneumonia is very different Table IV shows the incidence of pneumococcal types in two American series of cases of pneumonia

Similar results, in a smaller number of cases, were obtained by Glynn and Digby (1933) in Liverpool (England), as shown in Table V

TABLE V

INCIDENCE OF PNEUMOCOCCAL TYPES IN PNEUMONIA AND IN NORMAL SALIVA *

Pneumococci	Sputum from 127 cases of pneumococcal pneumonia		Saliva from 25 normal persons	
Type	Number	Per cent	Number	Per cent
I	48	37 8	0	0
II	28	22 0	0	0
III	2	1 6	0	0
Others	49	38 6	10	40
Total No of cases	127	100 0		

* After Glynn and Digby (1933)

Immunity

Specific immunity reactions occur in response to pneumococcal infections At or slightly before the time of defervescence, in cases of pneumococcal pneumonia, agglutinins, precipitins, opsonins and complement-fixing and animal-protective antibodies can often be demonstrated in the blood by appropriate methods A dermal reaction to specific soluble substance has been described by Tillett and Francis (1929), who found that, although patients early in the course of pneumococcal pneumonia showed no reaction to the intradermal injection of specific soluble substance, at the time of defervescence a large proportion showed an immediate urticarial and erythematous local reaction Potent protective sera against nearly all types of pneumococcus can be prepared , sera obtained from horses and from rabbits have been used therapeutically

The pathogenesis of pneumococcal pneumonia

Conclusions drawn from animal experiments

The now classical experiments of Blake and Cecil (1920) still provide the most convincing evidence of the probable mechanism of production of pneumococcal pneumonia in man They worked with Philippine monkeys, whose susceptibility to the pneumococcus seems more nearly similar to that of man than is the case with other animals that have been used in experimental studies By the intratracheal injection of minute amounts of virulent pneumococcal culture (generally

type I) they consistently produced a disease similar to lobar pneumonia in man. Spraying large amounts of pneumococcus culture into the nasopharynx failed to produce disease, although the organism was carried for at least a month. Intravenous injections of pneumococci failed to produce pneumonia, although they might cause death from septicaemia The blood stream was invaded in some cases during the course of the pneumonia caused by intratracheal injection of pneumococci.

The morbid anatomy of the pneumonia produced was similar to that observed in man From the study of animals killed at various intervals after infection, the authors concluded that pneumococci primarily invaded the pulmonary tissue near the hilum, probably by penetration of the bronchial walls, and then spread throughout the lobe in the perivascular, peribronchial and septal interstitial tissue and lymphatics, reaching the alveoli from the interstitial tissues The possibility that the primary invasion was by way of terminal bronchioles or alveoli near the hilum was not excluded, but it seemed certain that throughout most of the lobe the earliest lesions were interstitial, although, with the development of the later alveolar reaction, the early interstitial reaction was largely masked. The concept formed as a result of these experiments is that, once pneumococci of suitable virulence gain access to the lower respiratory tract, they can invade the interstitial tissue of the lung, and spread throughout a lobe or lobes, producing what may well be regarded as a cellulitis of the lung

Several authors have described experimental pneumococcal pneumonias in which the method of propagation of the inflammatory process through the lung appeared to be different from that described by Blake and Cecil, but in every instance in which an important deviation from their description has been observed, there was a complicating factor, absent from their experiments Thus Permar (1923) described experimental pneumonia arising as an acute inflammatory reaction in the trachea, bronchi, alveolar ducts and alveoli, causing lobular foci of consolidation which later coalesced, but he used rabbits, anaesthetized with ether, and injected with a volume of culture very much greater in relation to the size of the animal than that used by Blake and Cecil. Terrell, Robertson and Coggeshall (1933), using dogs, and Gunn and Nungester (1936), using rats, described an initial peripheral focus, from which the lesion spread by extension through the lung tissue and by the flow of oedema fluid along the smaller air passages In both these investigations, pneumococci were injected into the periphery of the lung suspended in a tenacious medium, starch being used by the former investigators, and mucin by the latter

Under these conditions, the initial lesion could not be expected to be of the same character as in the experiments of Blake and Cecil, inevitably being situated in the region in which the pneumococci had been injected in such a way that they were retained there Using the nomenclature of the pneumonias outlined above, the initiation of the pneumonic process in these experiments may be said to be by the " aspiration " mechanism, the earliest lesion being, in fact, an infected atelectasis, although its rapid spread to involve complete lobes of the lung was due to the specific activity of the pneumococcus It may be, of course, that pneumococcal pneumonia is initiated in a similar manner in some human cases,

pneumococci being aspirated into a peripheral bronchial branch in a plug of mucus; but in the cases which conform to the classical description of the disease, in having a sudden onset in persons previously in perfect health, it seems unlikely that this mechanism can be at work In any case, the essential property of the pneumococcus, in the initial stages of pneumonia, is its ability to spread rapidly through the lung causing inflammations of lobar or even multilobar extent.

or its products. It has been shown that pneumonia can be produced in animals by the endotracheal injection of substances to which the animal has been made hypersensitive, but the evidence concerning the importance of this factor, both in the human subject and in the experimental animal, is inconclusive. It has been suggested that the less definite onset and course of pneumococcal pneumonia in the infant, as compared with the adult, may be related to the fact that the infant has not been exposed previously to pneumococci, and thus has not become sensitized (Sharp and Blake, 1930, Lindau, 1933, Fried, 1933)

Atelectasis.—Coryllos and Birnbaum (1929) advanced the view that the first stage in the development of pneumococcal pneumonia is a pneumococcal bronchitis; this leads to obstruction of a main bronchus with tenacious mucus, and a lobar atelectasis results, which rapidly becomes infected with pneumococci. In dogs with experimental pneumonia they observed radiographic signs of atelectasis; but large volumes of culture had been injected into the trachea to produce the pneumonia, and the analogy with typical human pneumococcal pneumonia was thus probably false Attempts at treatment of human cases by carbon dioxide inhalations and bronchoscopic aspiration produced no convincing result in primary pneumococcal pneumonia Although there may be slight displacement of the mediastinum to the affected side and slight elevation of the diaphragm on this side in radiographs of pneumococcal-pneumonia cases, this is not a constant finding, and is much less than is observed in atelectasis It is, of course, possible that in the course of pneumococcal pneumonia small areas of atelectasis may develop, such areas are found at autopsy in many fatal cases, but their occurrence is to be regarded as a secondary phenomenon Atelectasis bears a much more direct relation to the "aspiration" pneumonias

Morbid anatomy

Distribution of the lesions

Whereas pneumococcal pneumonia in man typically assumes a lobar distribution in one or more lobes of the lung, a scattered lobular distribution also occurs, even in cases which are associated with a pure pneumococcal infection. A predominantly lobular distribution of lesions is most commonly seen in infants and in the aged; but in a high proportion, perhaps 20 per cent, of typically "lobar" cases, lobular foci can be found either radiologically during life, or at necropsy, in lobes other than those principally involved. There is some experimental evidence that variations in the relation between the virulence of the infecting pneumococcus and the resistance of the infected animal may determine whether the lesions assume a lobar or lobular distribution. Pneumococci of

es I and II rarely give rise to lobular lesions In some instances, it may be icult to distinguish clinically between primary pneumococcal lobular eumonias and less specific secondary diffuse aspiration pneumonias or secondary broncho-pneumonias" especially because pneumococci of the gher types may enter into the mixed bacterial flora of the latter group "Border-ne" cases, showing many of the characters of both groups, are frequent. nother difficulty arises in connexion with the pneumonias associated with nfluenza Pneumococci frequently play an important part in these pneumonias, which assume a confusing variety of forms, such pneumonias are considered among those associated with virus diseases

These considerations make it difficult to estimate the proportion of cases of primary pneumococcal pneumonia in which the lesions exist in scattered lobular foci Some idea of their relative frequency may be obtained from the figures of Tilghman and Finland (1937), of 1,586 cases of pneumococcal pneumonia, 15·5 per cent were regarded as "atypical", that is to say, lobular in distribution More definite information is available about the incidence of involvement of individual lobes in typical lobar cases Table VI shows the findings in a series of 1,896 clinical cases reported on by Cecil, Baldwin and Larsen (1927) No significant differences in the lobar involvement in cases due to various types of pneumococci were found

TABLE VI

LOBES INVOLVED IN 1,896 CASES OF PNEUMOCOCCAL PNEUMONIA *

Right-sided	Number	Per cent	Left sided	Number	Per cent	Bilateral	Number	Per cent
Right lower lobe	440	23 2	Left lower lobe	505	26 6	Right and left lower lobes	308	16 3
Right middle lobe	28	1 5	Left upper lobe	68	3 6	Three lobes (right and left)	82	4 3
Right upper lobe	117	6 2	Two left lobes	93	4 9	Four lobes (right and left)	29	1 5
Two right lobes	154	8 1						
Three right lobes	72	3 8						

* After Cecil, Baldwin and Larsen (1927)

Anatomical changes

The morbid anatomical changes in pneumococcal lobar pneumonia are conventionally divided into the four stages of engorgement, red and grey hepatization, and resolution, but the process is, of course, a continuous one At necropsy, different stages are generally found in different parts of the lung. The duration of these stages is not very well defined; in the absence of specific treatment, engorgement may last for about 12-24 hours, while red and grey hepatization probably last about 2-4 days each, and resolution occupies a very variable period, up to several weeks

Engorgement—The initial stage of engorgement is rarely seen except at the periphery of a spreading pneumonia, the lung is deep red in colour, heavy and moist, but still aerated. Microscopically, the alveolar capillaries are greatly distended, and the alveoli contain some serous exudate with a few red cells, pneumococci and leucocytes

Red hepatization—In the stage of red hepatization, the involved part of the lung is firm, friable, dark red in colour and airless, sinking in water. There may be an early dry fibrinous pleurisy. The cut surface is dry and granular;

a little reddish-brown fluid, containing minute granular masses from the alveoli may be obtained on scraping it with the knife The bronchi show, in typical cases, relatively slight changes, but they may be reddened and contain a little muco-purulent exudate Microscopically, the alveolar capillaries are still grossly distended, the alveoli are full of exudate, consisting of a coarse network of fibrin with many red corpuscles, polymorphonuclear leucocytes, pneumococci, and some large and small mononuclear cells. At this stage, all cells are clearly defined

Grey hepatization—In the stage of grey hepatization, the lung assumes a pinkish grey and then a whitish or yellowish grey colour, it becomes softer [illegible] the most numerous cells in the exudate, but some red cells and large mononuclear cells are still present Similar exudate may be seen in the terminal bronchioles The cells of the exudate at this stage are less well defined, apparently degenerating

Resolution—The stage of resolution is, for obvious reasons, rarely seen at necropsy except in scattered parts of an extensive lesion MacCallum (1932) described the gross appearance in 2 cases, in which large parts of the lung were seen in a stage of resolution, as translucent and yellowish, with blood vessels clearly distinguishable beneath the surface, the cut surface was moist and exuded a slimy yellowish fluid In the process of resolution, the alveolar exudate is removed and the lung becomes re-aerated and gradually returns to normal Microscopically, the most prominent feature is the increase in the numbers of large mononuclear phagocytic cells, or macrophages, which replace the degenerating cells of various sorts previously present in the alveoli The exudate is cleared from the alveoli by a complex process, first it is liquefied by autolysis, the ferments probably being derived from degenerating leucocytes, possibly aided by a local increase in acidity in the consolidated parts Then the liquefied exudate is removed, mainly by phagocytosis by the macrophages, very little, if any, being removed by expectoration It is generally agreed that these macrophages arise from cells normally present in the alveoli, although whether or not they represent a true alveolar epithelium is still a matter of dispute, they are probably identical with " dust cells " and " heart-failure cells " At the time of resolution, the hilar lymph-nodes become enlarged They are soft and succulent, and microscopically their sinuses contain many macrophages and lymphocytes and some polymorphonuclear leucocytes

Studies in experimental pneumonias of animals by various methods have indicated that there is some impairment of the blood circulation in pneumonic parts (Kline and Winternitz, 1915; Wang and Van Allen, 1900) Gross (1919) investigated the vascularity of human pneumonic lungs by post-mortem radiography after injection of radio-opaque fluid into the pulmonary vessels This showed a great diminution, both in the calibre of the smaller vessels of the pneumonic lobes, and in the number which were filled by the opaque medium It is probable that the circulation in the pneumonic lobe is impaired considerably more during grey than during red hepatization

Changes in other organs

In other organs, the changes associated with any febrile infective condition are found; among these may be noted soft "septic" enlargement of the spleen, and cloudy swelling in the liver, kidneys, myocardium, adrenal glands and pancreas.

In a few cases, the common early pleural reaction progresses to an exudative sero-fibrinous or fibrino-purulent pleurisy. Suppurative lesions in other organs, such as pericarditis, arthritis, peritonitis, meningitis and endocarditis, may be found These, as well as the less common modes of termination of the pulmonary lesion in abscess formation and organization, are discussed below.

Factors influencing susceptibility to pneumococcal pneumonia

Geographical distribution.—Pneumococcal pneumonia is of world-wide prevalence The death rates from "pneumonia" vary greatly, however, with locality. Certain tropical and sub-tropical areas have very high pneumonia death rates. Mexico and Central America, certain Indian cities, and Cairo and Alexandria in Egypt show high rates Lower rates than the average are found in western Europe, including the British Isles.

Season.—In most areas, there is a distinct seasonal variation in incidence, an increase being observed in the colder months In temperate zones, 60–70 per cent of the cases occur in winter and spring It has been shown that the proportion of persons carrying pneumococci in the nasopharynx increases during the winter Whether these increases in pneumonia incidence and in the numbers of pneumococcus carriers are directly due to seasonal changes is doubtful; they are probably both related rather more directly to the prevalence of predisposing epidemic respiratory catarrhal infections in the winter months.

[illegible] is somewhat greater at the [illegible] of the pneumonias [illegible] nature of bronchitic [illegible] ants, being specific pneumonias due to organisms other than pneumococci Considering pneumococcal pneumonia alone, it appears that there is a slightly preponderant incidence in early and middle adult life It is remarkable that the incidence of the different pneumococcal types in pneumonias varies at different ages; in children, as is shown in Table IV, type XIV is much more frequently found than in adults, and may in fact be the most frequent type in this age-group, whereas in adults type I is the most frequent.

Sex.—In all age-groups, pneumococcal pneumonia is commoner in males than in females In most hospital statistics, there are 2–3 times as many males as females; but some of this excess is due to the fact that a higher proportion of male patients with pneumonia are treated in hospital

Race.—This factor may have an effect on the incidence of pneumococcal pneumonia. Both in North America and in South Africa, the incidence and the mortality are higher among Negroes than among white men

Social conditions.—Such factors as overcrowding, malnutrition and exposure predispose to pneumonia. The death rates from pneumonia show a distinct inverse relation to the financial status of various social groups.

Occupation—Persons whose occupation involves physical labour in th
in all weathers, or exposure to frequent violent changes of temperature
dusty atmospheres show a special liability to pneumonia These ca
include general outdoor labourers, workers exposed to furnace heat, and
ground miners Special susceptibility to acute respiratory infections, in
pneumococcal pneumonia, exists in workers exposed to dusts containing ma
(manganese smelting, manufacture of potassium permanganate, and dry
industry) or to "basic slag" (a by-product of the Thomas and Gilchrist
of steel manufacture, used as an agricultural fertilizer)

Personal factors—Most individuals show a certain amount of natural im
to pneumococcal infection, least in infancy and increasing to a maximum i
life. Various factors may diminish this natural resistance These incl
exhaustion following unusual exertion, (2) exposure to wet and cold, or to
temperature variations, (3) chronic alcoholism or a bout of acute alco
and (4) malnutrition. The possible role of trauma in the aetiology of p
coccal pneumonia is doubtful, the commonest pulmonary complica
trauma to the chest wall is atelectasis of a lobe or lobes, which bears,
at least, no relation to pneumococcal infection.

Respiratory catarrhal infections.—In a very high proportion of cases of p
coccal pneumonia (probably more than 50 per cent), symptoms of an
respiratory catarrh precede the onset of pneumonic symptoms It is th
probable that the common cold and other epidemic respiratory catarrhs f
invasion of the lower respiratory tract by pneumococci In the case
common cold and of the ill-defined group of non-influenzal epidemic c
there is no evidence that the causative agents can themselves descend to t
and take part in the production of the lung lesions. Thus there is no re
suppose that pneumococcal pneumonia following such upper-respirator
tions is other than a pure pneumococcal infection In true epidemic in
there is good evidence that the virus can and does play a part in the pro
of lung lesions, hence, although the lung lesions of epidemic influenza a
infected with pneumococci, they are best considered as part of the rather
geneous group of "pneumonias associated with influenza"

Conveyance of infection—The problem of the relative importance of exo
and endogenous infection in pneumococcal pneumonia is complicated A
above, pneumococci are common inhabitants of the upper respirator
over 50 per cent of the subjects investigated usually being found to
them Because these pneumococci are mostly of the higher types, the q
arises: "How important is fresh infection with a new and virulent
determining the onset of pneumonia?" Several investigations have
that, in persons who have been contacts of patients with pneumonia, pneu
of the types causing the pneumonias are found rather more frequently
upper respiratory tract than in persons who have had no such contac
in the limited numbers investigated, no increased incidence of pneumonia
the contacts could usually be detected Thus, Rosenau, Felton and
(1926) found type I pneumococcus in 8 1 per cent of persons who had
contact with cases of type I pneumonia, but in only 2 2 per cent of those w

had no contact with cases of pneumonia They could find no history of the source of infection in the carriers of the "non-contact" group Occasional cases of apparent direct contact infection have been reported as have a few small local outbreaks of pneumonia due to a single type of pneumococcus; more extensive outbreaks of pneumonia associated with a single pneumococcal type may occur in enclosed communities at the time of respiratory catarrhal epidemics, especially influenza, but these present a different epidemiological problem. The increased incidence of pneumonia in the community in general during the colder season, or at the time of respiratory catarrhal epidemics, is associated with a variety of types of pneumococcus It may be that, in pneumonias associated with the higher types, infection is most frequently endogenous in origin; in those associated with types I and II, and possibly also V, VII and VIII, the disease may more often directly follow the acquisition of new type of pneumococcus in the naso-pharyngeal flora.

Symptoms of pneumococcal pneumonia

The following description of the symptoms is based mainly on the picture presented by patients not treated by specific measures, the course of the disease is profoundly altered by sulphonamide or antibiotic treatment.

Onset—As noted above, in over 50 per cent of cases there is a history of a precedent upper-respiratory catarrhal infection. but, apart from this, the onset of the pneumonia itself is sudden and dramatic in most cases. The cardinal symptoms at the onset are rigor, pleuritic pain, fever, cough and "rusty" sputum In over 50 per cent, a rigor or less clearly defined chilly sensation, with a feeling of weakness and malaise, leads to an abrupt rise of temperature, reaching 102–104° F within a few hours; pain, dyspnoea, cough and sputum generally appear within the first day Sometimes, the first definite symptom is pleuritic pain Headache and anorexia are common early symptoms; in a few cases vomiting may occur at the onset About 75 per cent of patients can refer the onset of their serious symptoms either to a rigor or to a pleuritic pain; in the rest, a gradually increasing malaise, often accompanying an upper-respiratory catarrhal infection, leads to the gradual development of more definite symptoms.

Fever—In previously healthy vigorous individuals, the temperature rises either suddenly with a rigor, or more gradually with the less definite modes of onset, to reach a level of from 102° F to 106° F by the second day. It is then maintained at a fairly constant high level,
In untreated cases with recovery, deferve
fifth and the ninth day, but may occasion[illegible]
or even later. In slightly over 50 per cent of cases, defervescence occurs by crisis: that is, by a sudden fall of temperature, and of pulse and respiration rates, with rapid clinical improvement, occurring within 24 hours Towards the end of the period of maintained pyrexia (or fastigium) the temperature may show an increased diurnal variation, and in cases with defervescence by crisis the chart may show a temporary fall to normal, without corresponding clinical improvement, on the day preceding the true crisis: this event is called a "pseudo-crisis". Defervescence by smaller steps, extending over 36 hours or more, is termed lysis. The pulse rate in favourable cases is raised in proportion to the rise in temperature.

In aged or debilitated persons, the febrile --
be lower h· · ·

. ..spiration rate is always raised, though to a variable level. Rates of from 26 up to 40 or 50 per minute in adults, and even more in infants and young children, are commonly observed The degree of respiratory distress varies greatly. It is, for obvious reasons, greater when pleuritic pain is severe Some degree of cyanosis is usually present, it is greater in asthenic patients or in those with an accompanying bronchitis, but is, in general, not so severe in uncomplicated pneumococcal pneumonia as it is in diffuse bronchitic aspiration pneumonias

Pain.—Pain in the chest is a frequent early symptom, and occurs at some time during the course of most cases Most characteristically, it is of pleuritic type, sharp and stabbing, aggravated by breathing or cough, and is then referred to the chest-wall over the affected area Occasionally, diaphragmatic pleurisy causes pain referred to the shoulder-region and abdomen, and may cause ·
difficulty Sometimes, pain is of a less def
as a deep aching soreness Pain, of
in severity in most cases as the dise

Cough - ·
but
bloo
cases
In elderly asthe ... which
has been descri ... produced The daily amount of sputum varies ... in infants and young children, and even in some adults, the sputum is swallowed, so that none is produced throughout the course. In bronchitic subjects, the characteristic sputum may be masked by admixture with frothy muco-purulent bronchial secretion In about 25 per cent of cases the sputum shows no characteristic appearance at any time Microscopically, the typical rusty sputum contains pus cells, red blood cells and Gram-positive diplococci, in the less typical sorts of sputum, a great variety of bacteria may be seen

Nervous symptoms—Headache, restlessness, insomnia and some mental confusion are almost constant symptoms In about 25 per cent of cases disorientation and delirium occur In alcoholic subjects, delirium tremens may appear at the onset of pneumonia

Gastro-intestinal symptoms—Appetite is lost, the tongue is furred, and the bowels are costive, there may be nausea and, more rarely, vomiting Meteorism or hiccough are occasionally troublesome In 5–10 per cent of cases ·
detectable jaundice develops, probably due to
from increased blood ·

Termination ... time at which death occurs is from ... eighth day of the illness, it may occur as early as the second day, or be delayed until the third or fourth week. Death usually

approaches insidiously. The pulse becomes progressively more rapid and feeble, and may be irregular ; the blood pressure falls, respiration becomes shallow and rapid, cough is ineffective and finally ceases, sputum collects in the air-way, and progressively increasing cyanosis gives place to greyish pallor.

In favourable cases, malaise, restlessness and insomnia are diminished, and pulse and respiration rates fall in step with the fall in temperature—rapidly in cases with defervescence by crisis, more gradually with lysis. Sweating often occurs with defervescence, especially by crisis Crisis is commoner in vigorous adults than in the aged, in children or in the debilitated , it is more common in infections with types I and II pneumococcus than with other types. After defervescence, symptomatic improvement is generally rapid The temperature often falls to a little below normal for a day or two, and there may be slight bradycardia

Other modes of termination—delayed resolution, organization and abscess-formation—are discussed under " Complications ".

Physical signs

General aspect

Quite early in the disease, the patient appears acutely ill, flushed and more or less cyanosed The skin is hot and dry ; there are tachypnoea and some respiratory distress but generally no orthopnoea , the alae nasi dilate on inspiration, especially in children There may be a short pause at the end of inspiration, ending in a soft grunt at the beginning of expiration, whereas in health a pause occurs at the end of *expiration Herpes appears around the lips and nose about* the second or third day in 33 per cent or more of cases There may be obvious anxiety, restlessness or mental confusion.

The chest

[illegible] arrangement of the lobes of the [illegible]

indicate lower-lobe lesions , signs anteriorly and at the apex only indicate upper-lobe lesions , signs just above the area of hepatic dullness, anteriorly on the right side, indicate middle-lobe lesions.

[illegible] ment of respira- [illegible] after cough [illegible] d or increased. Very [illegible] ign

Signs of consolidation—The characteristic signs of consolidation generally do not appear until the second or third day On inspection, the affected side of the chest moves less, the degree of this diminution depending upon the severity of the pleural pain On palpation, there is increased vocal fremitus over the *consolidated area in most cases , very occasionally* a pleural friction-rub may be palpable. In uncomplicated cases, no displacement of the heart's apex beat is detected. On percussion, there is distinct impairment of note over the consolidated

lobe or lobes. This impairment rarely reaches complete dullness, the presence of which should cause suspicion of the presence of pleural fluid, although, over some of the pneumonias associated with influenza, dullness may be almost stony. In pneumonia of lobar distribution, the area of dullness corresponds roughly with the surface-marking of the affected lobe. On auscultation, the characteristic change is the presence of high-pitched bronchial breath sounds, usually described as tubular. These sounds may be striking in their intensity, but in some cases less definite changes in the breath-sounds may be noted. Occasionally, breath-sounds may be weakly bronchial in character or even be absent over the affected lobe; this may be due either to a thickened pleura caused by thick fibrin deposits in dry pleurisy, to the presence of pleural fluid, to a rather moist oedematous consolidation, or to the presence of much secretion in the bronchi. In the last-mentioned event, an effective cough may lead to the return of frank bronchial breath sounds. Accompanying the bronchial breath sounds, there [illegible]

[illegible] increased, and whispering pectoriloquy is often heard. In the cases in which the breath sounds are weakly bronchial in character, voice conduction may be aegophonic.

Resolution.—After defervescence, the first change in the physical signs is the reappearance of fine râles, which are termed redux crepitations. The dullness and bronchial breath sounds usually persist unchanged for several days, they then gradually diminish in extent and in intensity. The duration of persistence of abnormal signs is very variable, corresponding to the very variable rate of resolution. In most cases, the more obvious signs disappear by the end of the second week after defervescence, the most persistent signs are usually a slight impairment of percussion note and crepitant râles on deep inspiration or after cough.

Cardiovascular system

In most cases distinctive cardiovascular signs are not found. The pulse rate is increased in proportion with the temperature. No displacement of the heart's apex beat or change in the area of cardiac dullness can generally be made out. Radiography shows slight enlargement of the cardiac shadow in a small proportion of cases.

The heart.—The position of the apex beat, however, is important both in differential diagnosis and in the diagnosis of complications that may arise, such as empyema, delayed resolution or pericarditis. There may be a systolic murmur which disappears after recovery, as in other febrile diseases.

The blood-pressure shows no very striking change in favourable cases; it tends to rise slightly in the acute stages, and the pulse pressure may be rather high.

Abnormalities of cardiac rhythm are observed at some stage in 10–20 per cent of cases. In most of these, the abnormality consists only in auricular or ventricular extrasystoles, probably of little significance. In 5 per cent or less, the abnormal rhythm takes the form of auricular fibrillation or flutter, which may be persistent or paroxysmal. These are of more serious significance; their incidence is

predominantly in older patients, in whom arteriosclerotic changes are probably present, and in patients with pre-existing cardiac disease Congestive heart failure is extremely rare in pneumococcal pneumonia, except in patients with pre-existing cardiovascular disease

Peripheral vasomotor disturbances

The principal effect of the disease on the cardiovascular system seems to be on the peripheral vasomotor mechanism Both clinical observation in uncomplicated cases and histological examination in fatal cases give little evidence of serious effects on the myocardium; but there is evidence of impairment of the contractile power of minute blood vessels, which persists for some weeks after defervescence (Perry, 1934). It seems likely that the final circulatory collapse in fatal cases, manifested by falling blood pressure, rising pulse rate, and cold clammy cyanosed extremities, is due to a peripheral vasomotor failure, probably of toxic origin

Alimentary system

In straightforward cases, no abnormal sign is present except a furred tongue Abdominal distension and meteorism may occur In some cases, not only may pleural pain of diaphragmatic origin be referred to the abdomen, but a corresponding abdominal-muscle rigidity may add to the diagnostic difficulty

Nervous system

In many cases the tendon-jerks are diminished or absent Very rarely, in children and especially with upper-lobe consolidations, meningism is present. The occurrence of delirium is noted above

Laboratory examinations

Urine

Febrile albuminuria, usually transient, is observed in most cases. In a few cases, casts and even red cells appear during the febrile stage, but rapidly disappear after defervescence, without evidence of deficient renal function at any time The rare occurrence of more serious renal damage is discussed under " Complications " The specific soluble substance of the pneumococcus may be detectable in the urine, especially in severe cases , it may continue to be excreted for several weeks after defervescence During the febrile stage, the excretion of chlorides in the urine is much diminished or ceases, and that of sodium also diminishes while that of potassium increases After defervescence, chlorides are excreted in a temporarily increased amount

Blood

Blood count —Leucocytosis of between 20,000 and 40,000 cells per cubic millimetre appears in a large proportion of cases within a few hours from th onset, and is often maintained at a fairly constant figure during the febrile stage The polymorphonuclear neutrophils are generally 80–90 per cent of the tota After defervescence the count in uncomplicated cases drops gradually to norm in a week or 10 days At the time of defervescence, the proportion of monocyt may increase The blood platelets diminish and the coagulation time is prolong

in the acute stages Both return to normal after defervescence, the platelet count may rise above normal for a few days before finally settling to its normal figure

Blood culture—In from 20 to 40 per cent of all cases pneumococci can be cultured from the blood The incidence varies with the age of the patient and with the type of infecting pneumococcus Bacteraemia occurs in children and adolescents somewhat less frequently, and in the aged more frequently, than it does in adults Positive blood cultures are obtained more frequently after the fourth day; the number of cases in which bacteraemia is detected is (as would be expected) greater when repeated cultures are made The influence of bacteraemia on mortality and on the incidence of complications is discussed below

Blood chemistry

Oxygen saturation—The arterial blood shows incomplete oxygen saturation [illegible] ponds roughly with the degree of cyanosis present There are several possible factors in its causation: (1) interference with oxygen exchange in the alveoli by exudate, (2) shallow rapid breathing, (3) passage of blood through vessels in consolidated and therefore unaerated parts of the lung, and (4) acceleration of blood flow through normal parts of the lung These factors are probably operative in varying degrees in different stages of the disease In the early spreading stage, interference by exudate in the alveoli with oxygenation of blood passing through the affected part may be important, this poorly oxygenated blood mixing with that coming from more normal parts Later, as is mentioned above, the blood circulation in the affected parts becomes much restricted, and a smaller proportion of the total circulation passes through unaerated parts, the factor of admixture of imperfectly oxygenated blood becomes less important The rapid shallow breathing, which is present throughout the course of the disease, may be produced by a more or less voluntary inhibition of respiration on account of pleuritic pain, it may be caused by the increased rigidity of the consolidated lung, leading to the premature inhibition of inspiration by the Hering-Breuer reflex, or it may possibly be due to a toxic effect on the medullary centres This rapid shallow breathing is inefficient, both because the ratio of tidal air to dead-space air is much reduced, and because it leads to unequal aeration of alveoli, with consequent inefficient oxygenation of the blood passing through the less well aerated alveoli Clinically, it may be noted that cyanosis is most severe with a rapidly spreading lesion, or with evidence of excessive bronchial secretion in the more normal parts of the lung, it is, on the whole, of less severe grade than may be seen in the more serious cases of diffuse aspiration pneumonia (secondary broncho-pneumonia)

Carbon dioxide—The carbon dioxide content of the blood is slightly reduced, probably on account of the rapid shallow breathing which is more effective in disposing of carbon dioxide than it is in acquiring oxygen

Salts—The chloride content of the blood diminishes It may fall from its

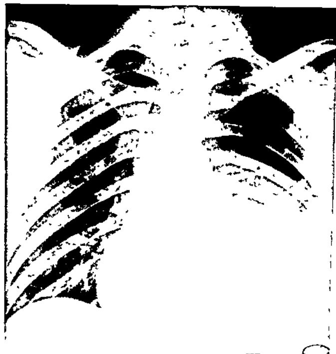


FIG. 26.—Radiograph of lobar consolidation of left lower lobe

FIG 27.—Same case as in Fig 26, lateral view.

normal figure of 350–380 milligrams per 100 millilitres of plasma to a figure as low as 280–300 milligrams, or, expressed as sodium chloride from about 600 milligrams per 100 millilitres to about 480 milligrams The blood sodium also diminishes, as does the total base, while the potassium is somewhat increased. Since, as noted above, the chloride excretion in the urine diminishes in the acute stage, and the loss of chloride in the sweat and sputum is quite insufficient to account for its diminution in the blood, it appears that the chloride ion is retained in the tissues After defervescence, normal blood chemistry is rapidly restored The significance of these changes is not clear Attempts have been made to restore more normal conditions by administration of salt, but this measure fails to raise the plasma chloride Oedema develops if excess of salt is given, as would be expected, since the evidence suggests that the extra salt is being stored in the tissues

Radiographic appearances

Early changes—Changes are generally evident in the radiograph within 24 hours from the clinical onset, and are probably never delayed beyond 48 hours The earliest change in most cases is an opacity which, in the antero-posterior view, extends out from the hilar region into the affected lobe. The margin of this early shadow shades off gradually into the as yet unaffected part of the lobe, into which it spreads in the course of a day or so In a minority of cases, the opacity is at first peripheral in the antero-posterior film, and then spreads inwards towards the hilum , this is observed more frequently in children and in pneumonias [illegible]

of the lower lobe.

Consolidation—Fully developed lobar consolidation appears as an opacity [illegible]

raised on the affected side, and slight displacement of the heart towards the affected side may be detected radiographically, although it is not detectable clinically Pneumonic consolidation is distinguishable from atelectasis by the absence of contraction of the affected lobe, and by the consequent absence of such gross displacement of mediastinum, diaphragm or chest wall as is seen in the latter condition As with atelectasis, examination in the lateral view may be necessary to determine the exact relation of the shadows observed to lobes, especially with lesions appearing in the middle zone of the right lung in the antero-posterior view Radiography frequently reveals small areas of consolidation in other lobes than those principally affected

Resolution—In normal resolution, the opacity generally disappears in uneven fashion, leaving irregular clear areas which sometimes suggest cavity formation The part of the opacities near the hilum is usually the last to disappear. With the onset of resolution, swelling of the broncho-pulmonary lymph-nodes on both sides may be observable The time required for the completion of resolution varies

greatly, from about a week up to 6 or 7 weeks ; resolution may rarely be delayed as long as 12 weeks, yet eventually be complete

Radiological studies of pneumococcal pneumonia have been made by Davies, Hodgson and Whitby (1935) and by Graeser, Wu and Robertson (1934).

Variations in the clinical picture

Atypical or lobular pneumococcal pneumonia.—Pneumococcal pneumonia may appear in scattered lobular distribution, especially if it is due to infection by one of the higher types, also in infants and young children It is impossible, and indeed pointless, to attempt to draw a hard-and-fast line between lobar and lobular, or typical and atypical cases As is noted above, typical lobar pneumococcal pneumonias frequently show radiological evidence of lobular involvement in lobes other than those principally affected In cases showing predominantly [illegible]

[illegible] frequently insidious, the temperature curve is less regular in form, and defervescence is more often by lysis Physical signs of gross areas of consolidation are not found , the only abnormal findings may be ill-defined areas of impaired percussion, with fine to medium râles and inconstant isolated areas of bronchial breath sounds Radiography shows patchy areas of increased density, most usually in one or both lower lobes Since these atypical cases often occur in the course of some other disease, either of the respiratory tract and elsewhere, the distinction between them and the less specific diffuse aspiration pneumonias may be difficult

Abortive pneumonia.—In all large series of cases of pneumococcal pneumonia, a few (about 1 per cent of the total) are observed, in which, after a characteristic onset, the patients recover within 2 or 3 days without specific treatment

Pneumococcal pneumonia in infancy and childhood.—The difference between the incidence of pneumococcal types in the pneumonias of children and of adults is noted above The great frequency of type XIV infections in children is especially noteworthy, although no explanation of it has been found. In the new-born infant, pneumonia of lobar distribution is occasionally seen, but it is most often due, not to pneumococci, but to staphylococci, streptococci or *Bacterium coli* The very rare cases of pneumococcal pneumonia at this early age are observed most frequently in association with pneumococcal pneumonia in the mother. Later in infancy, the pneumococcus is the most common cause of pneumonia, and usually causes a pneumonia of lobular distribution The clinical picture may differ from that seen in adults in several respects An initial rigor is rare. Convulsions may occur at the onset Vomiting and diarrhoea may be important symptoms The characteristic sputum is not observed, for children rarely expectorate, but swallow their sputum The appearance of physical signs is generally delayed, and early radiography is therefore of value in diagnosis Clinically, the diagnosis is suggested by an acute onset, fever, characteristic rapid respiration with an expiratory grunt and action of the alae nasi, cough, and

Complications

The complications of pneumococcal pneumonia fall into three main groups. The first is composed of local complications, such as empyema, delayed resolution, abscess-formation and organization; the second consists in suppurative conditions in parts of the body other than the lungs, mostly in serous membranes, such as pericarditis, endocarditis, peritonitis, meningitis and arthritis; the third includes toxic affections of other organs, such as nephritis and jaundice. The incidence of most of the complications, and especially of inflammations of serous membranes, including empyema, is very much higher in cases in which bacteraemia is detected. Thus, Tilghman and Finland (1937) found that, of 582 bacteraemic cases, 159 (27 per cent) showed complications, whereas in 1,004 non-bacteraemic cases, complications occurred in only 119 (12 per cent).

Local complications

Incidence of empyema.—Pleurisy is a nearly constant finding in pneumococcal pneumonia. In most instances, it remains of a dry fibrinous type. Undoubtedly, some serous exudation occurs in a high proportion of cases, but it gives rise to no detectable change in the physical or radiographic signs. The cytology of these fluids has been investigated by Scott and Finland (1934). They found that, in thin fluids which remained sterile the predominating cells at first were active polymorphonuclear leucocytes, the number of these diminished until, at the end of about a week, monocytes and macrophages and, later still, lymphocytes appeared. In a few cases of persistently clear effusions an eosinophilia was noted in the fluid during the third week or later. If the fluid became purulent and infected, the polymorphonuclear leucocytes became inactive and degenerated. Clear effusions, large enough to attract attention clinically, have become more frequent since the use of sulphonamides and penicillin became general. In

and persistently contains a preponderance of lymphocytes, revision of the original diagnosis of pneumococcal pneumonia should be considered. The incidence of purulent effusions (or of ... 2 to 5 per cent in most clinical series of cases befc ... and is probably less now.

Symptoms of empyema.— ... continuous with those of the pneumonia, fever persisting in spite of adequate specific treatment and often assuming a swinging type; alternatively the temperature may settle, and then after a few days rise again with the development of the empyema. With this persistent or recurrent fever, there is sweating, loss of weight, and persistent leucocytosis.

Diagnosis of empyema.—The differential diagnosis from delayed resolution may be difficult. Physical examination will show persistent dullness at the base of the affected lung: it may be observed to be more intense than was observed ... area of dullness

position from the beginning, and in these cases the area of dullness cannot assume the usual shape E [illegible] if the lung under t [illegible] may be heard clea [illegible] breath sounds become weak or absent over the empyema The voice conduction may remain increased, it may become aegophonic, or it may be diminished. Hence auscultatory signs may be of little value in differential diagnosis. Radiography may help, but with a consolidated lung under a small or moderate-sized empyema the changes may not be conclusive Lateral or oblique views are often desirable [illegible] be performe [illegible] signs are m [illegible] single criterion The most frequent error in needling for empyema is to insert the needle too low ; the fifth or sixth intercostal spaces in the mid-axillary line, or the seventh or eighth in the scapular line are the most favourable for an unlocated empyema A needle of adequate bore must be used, for the pus in a pneumococcal empyema is frequently thick and full of masses of fibrin Rarely, an empyema develops on the opposite side to that principally involved in the pneumonic process

Lung abscess—The full clinical picture usually associated with lung abscess is seen so rarely after pneumococcal pneumonia that the generalization might be made, that septic lung abscess is not a complication of pure pneumococcal pneumonia However, macroscopic areas of suppuration may be seen on the cut surface of the lung in about 5 per cent of fatal cases ; the appearance of clear areas in the shadow of the resolving lobe, suggesting cavitation, is mentioned above The interpretation of these is often doubtful, but in some cases an undoubted fluid level may be seen, and there seems to be no reason to doubt that cavitations occurring during resolution of pneumococcal pneumonia are usually due to pure pneumococcal suppuration They produce no clinical symptoms or signs, and may be regarded as incidental necropsy or radiographic findings When discovered by radiography during life, such lesions are almost invariably found to heal rapidly as resolution proceeds, without necessitating special treatment, leaving remarkably little residual change The only clinical importance of this condition is that undue alarm may be felt if a cavity is observed radiographically during the course of resolution The occurrence of clinically obvious suppuration in pneumonias due to other organisms, such as Friedlander's bacillus and *Staphylococcus aureus*, and the relation of pulmonary abscesses to the aspiration pneumonias are discussed below.

Delayed resolution—It is noted above, in discussing radiographic appearances, that, whereas resolution is usually complete within 2 or 3 weeks, it may occasionally be delayed as long as 12 weeks, and yet the lung may return to normal as far as can be determined by clinical and radiographic examination In delayed resolution, the residual symptoms—such as cough and expectoration, slight pyrexia and continued weakness—are generally much less remarkable than the residual physical signs and radiographic changes Factors which have been shown to be frequently associated with delayed resolution include previously existing

chronic pulmonary diseases, such as chronic pulmonary tuberculosis, bronchiectasis and pneumoconiosis, and old calcified tuberculous lesions of the broncho-pulmonary lymph-nodes This is in accordance with expectation, since the pneumonic alveolar exudate is removed chiefly through the lymphatic vessels of the lung The principal importance of delayed resolution rests in its differential diagnosis. The difficulty presented in distinguishing it from *empyema* is mentioned above. Tuberculosis, bronchiectasis, and bronchial obstruction by a neoplasm or a foreign body must also be considered in differential diagnosis Appropriate bacteriological examinations, serial radiography, bronchography or bronchoscopy may be necessary.

Organization —If the exudate is not removed normally from the alveoli after defervescence, it may become organized by the out-growth of fibroblasts from the alveolar walls If this process is extensive, it leads to the conversion of the affected part of the lung into a dense airless vascular mass of scar tissue; the condition of the lung is then termed carnification In its fully-developed form, carnification following pneumococcal pneumonia is so rare as to constitute a pathological curiosity; but in fatal cases small areas in which the exudate is organizing are not infrequently found histologically. Clinically, evidence of a significant amount of residual fibrosis after pneumococcal pneumonia is very rarely found

Suppurative conditions in other parts of the body

Pericarditis —Pericarditis is found in about 10 per cent of fatal cases, a larger proportion than would be suspected from clinical findings It occurs most frequently in seriously ill patients near the end of their illness, and thus may not produce any clearly distinguishable symptoms It is usually associated with empyema The principal pathognomonic signs are a pericardial friction rub, usually first heard over the base of the heart, or with a pericardial effusion, enlargement of the area of cardiac dullness with *increasing* engorgement of the neck veins

Acute endocarditis —Endocarditis due to the pneumococcus is a rare and serious complication, it is found at about 5 per cent of necropsies, but can rarely be diagnosed during life It appears to be commoner with type II *infections*. In about 50 per cent of cases there are pre-existent cardiac lesions. The vegetations are usually soft and friable, the right side of the heart is more often attacked than in acute endocarditis caused by other organisms, and there may be mural vegetations Acute endocarditis may be suspected clinically if there is delay in defervescence associated with a persistently positive blood culture; as with other forms of infective endocarditis, there may be multiple embolic lesions, manifested by purpuric spots, splenic enlargement, haematuria and so forth. Meningitis is associated with the endocarditis in some cases. Although changes in cardiac murmurs, and the appearance of new murmurs, especially in diastole, are of importance in diagnosis, in some cases no definite clue is obtained from examination of the heart.

Meningitis.—Meningeal involvement is found in about 1 in 40 fatal cases of pneumococcal pneumonia The clinical symptoms and signs are similar to those of meningitis due to other pyogenic organisms, and the diagnosis can be made

with certainty by examination of the cerebrospinal fluid. This shows an excess of polymorphonuclear leucocytes, which may be sufficient to make the fluid macroscopically purulent, and pneumococci can be found both by direct examination and by culture

Arthritis —Purulent arthritis has been reported to occur in between 1 in 200 and 1 in 500 of all cases without specific treatment, but it is now very rare It usually affects a single large joint, though several may be affected simultaneously or successively The diagnosis can be confirmed by examination of fluid aspirated from the affected joint. Although occasionally a case is seen in which the fluid, though purulent, contains no viable pneumococci, and the condition resolves after aspiration, in most cases pus forms

Peritonitis —Pneumococcal peritonitis is observed in about 1 in 40 of fatal cases, and in large unselected series of cases it has been reported in about 1 in 500 The severe abdominal pain and discomfort which may be caused by simple meteorism may closely mimic the symptoms of peritonitis. Paracentesis may be necessary to establish the diagnosis Primary pneumococcal peritonitis may occur, especially in female children, without pneumonia

Otitis media —Infection of the middle ear, due to the infecting type of pneumococcus, is more frequent as a complication of pneumococcal pneumonia in children than in adults With appropriate treatment, it does not seem to influence the prognosis Very occasionally, the otitis media may progress to acute mastoiditis

Conjunctivitis —This is an occasional complication, which has little effect on the prognosis It usually responds rapidly to local treatment

Acute parotitis —Although a recurrent form of parotitis due to pneumococci is recognized, it rarely occurs in association with pneumonia In pneumococcal pneumonia, as in other febrile illnesses, acute parotitis is a possible complication, but it is usually caused by other organisms, especially *Staphylococcus aureus*, and the most important predisposing factor is faulty oral hygiene

Toxic affections of other organs

Jaundice —Jaundice, usually mild, can be detected in 5–10 per cent of cases It is probably due partly to toxic depression of liver function, which is associated with the cloudy swelling of the liver cells, observed microscopically in fatal cases, and partly to increased destruction of blood In a small number of cases, a more profound jaundice appears This is usually an accompaniment of a severe infection, and to this extent is an unfavourable prognostic sign, but if the pneumococcal infection is overcome, the hepatic damage is not permanent and recovery is complete

Acute nephritis —Whilst evidence of toxic effects on the kidneys is provided by the frequent finding of albuminuria, and by the presence of cloudy swelling in the kidneys in about 50 per cent of fatal cases, a definite acute nephritis is a rarity It may escape clinical diagnosis, for it tends to appear in severely ill patients Rarely, however, the onset of acute nephritis is recognized either during the febrile period or shortly after defervescence; increased albuminuria, haematuria, cylindruria and oliguria, accompanied by oedema and evidence of nitrogen retention, and possibly by headache and vomiting, are the chief

manifestations. In patients recovering from the pneumococcal infection, the accompanying acute nephritis generally has a benign course, with complete resolution within a few weeks or months, but cases of permanent and progressive renal damage are recorded.

Rarer complications—Acute dilatation of the stomach, peripheral neuritis, thrombophlebitis of peripheral veins, and pneumococcal abscesses in various situations are among the rarer complications.

Differential diagnosis

Pneumococcal pneumonia may be confused (1) with various extrapulmonary acute infections, (2) with certain other acute intrathoracic conditions, and (3) with other forms of pneumonia.

Extrapulmonary diseases

Appendicitis—Simulation of acute abdominal conditions, especially appendicitis, by pneumococcal pneumonia is possible because of the reference of diaphragmatic pleural pain to the abdomen, through the lower intercostal nerves; tenderness and increased muscular resistance may also be present, and if, in addition, there has been vomiting at the onset, the simulation of appendicitis may be very close. The difficulty arises more frequently in children than in adults. The patient with pneumonia usually looks more ill; his pulse and respiration are more rapid, in addition to the abdominal pain there may be shoulder pain (though this is not constant); the leucocyte count is higher in the early stages; abnormal physical signs in the chest should be detectable, finally, in doubtful cases, a radiograph of the chest should be taken

Meningitis—Sometimes at the onset of pneumonia, more especially in infants and young children, signs suggestive of meningeal irritation may be found, such as severe headache, convulsions, vomiting, head-retraction and even Kernig's sign. These exaggerated nervous symptoms are commonly stated to be more frequent with upper-lobe pneumonias The detection of abnormal signs in the chest, aided by radiography if necessary, and, in cases which remain doubtful, the finding of a normal cerebrospinal fluid, determine the diagnosis

Acute fevers.—Certain acute fevers, such as scarlet fever and typhoid and typhus fevers, may simulate pneumonias at their onset, but are soon differentiated by their course.

Acute intrathoracic conditions other than pneumonias

Pulmonary infarction—Pulmonary infarction, caused by peripheral pulmonary embolism may cause difficulty The symptoms appear some time after embolism of a medium-sized or small branch of the pulmonary artery, and are not always dramatically sudden in onset Rigor with sudden rise of temperature is much more suggestive of pneumonia, whereas frankly blood-stained sputum and the presence of a predisposing condition, such as heart disease, a previous operation, obvious venous thrombosis, or tenderness of the calves, favours the diagnosis of infarction Pulmonary infarctions are often recurrent, and evidence of right-sided heart failure, either from a large embolism or from multiple smaller ones, may appear. Finally, the absence of pneumococci from the sputum in infarction of the lung

may be helpful in differentiation The physical and radiographic signs of the two conditions may be identical

Tuberculous pleurisy—In those cases of tuberculous pleurisy with effusion in which the onset is sudden, the clinical picture may closely resemble that of an acute pneumonia A definite rigor at the onset and the appearance of rusty or slightly blood-stained sputum favour the diagnosis of pneumonia Later, the physical signs and course rarely leave doubt of the diagnosis At the onset, the shape of the area of dullness, reaching its highest point in the axilla with an effusion, is a helpful point In doubtful cases, a diagnostic paracentesis should be performed The points of distinction between a primary pleural effusion and an effusion complicating a pneumonia are mentioned above

mind The cardinal sign is the displacement of the heart, which is easily detectable clinically in atelectasis

Atelectasis caused by pericarditis—Acute pericarditis, either rheumatic or tuberculous, may give rise to abnormal signs in the left lower lobe, closely resembling those of pneumococcal pneumonia, presumably produced by atelectasis of part of this lobe The diagnosis of pericarditis may be suggested (1) by a history of preceding or concurrent rheumatic manifestations, cardiac or otherwise, (2) by central thoracic pain, (3) by tachycardia, dyspnoea and cyanosis, and venous engorgement, out of proportion to the lung signs, (4) by the presence either of pericardial friction, or of enlargement of the area of cardiac dullness with distant heart sounds

Differentiation from other forms of pneumonia

Other bacterial pneumonias—The diagnosis from many of the other acute specific bacterial pneumonias can be made with certainty only by bacteriological studies Clinical points of differentiation are mentioned in discussing the other bacterial pneumonias Acute tuberculous pneumonia may mimic pneumococcal pneumonia in its onset, and it is only after failure to respond to sulphonamides and penicillin that suspicion may be aroused, the appearance of tubercle bacilli in the sputum may be delayed for some weeks

Influenzal pneumonia—The pneumonias associated with influenza cannot be diagnosed with confidence clinically unless there is evidence of the primary disease, but they present certain clinical differences from simple pneumococcal pneumonia, which are discussed below

Virus pneumonias—The diagnosis of virus pneumonias depends eventually upon laboratory studies; clinically, the onset tends to be with constitutional and febrile rather than respiratory symptoms, in contrast with pneumococcal pneumonia, in which cough and pleurisy are early symptoms

Aspiration pneumonias—The symptoms in the diffuse varieties of aspiration pneumonia arise insidiously, either as a gradual intensification of those of a bronchitis, or in a patient ill from some other disease, whereas in the localized types complicating acute respiratory infections in relatively vigorous persons, symptoms may be very mild The physical signs are very rarely those of lobar

consolidation. The course is very variable. The principle criterion, however, is the bacteriology of the sputum, which in these cases shows a mixed "normal" flora, in which pneumococci usually are not present at all or there may be at most a small number of pneumococci of one of the higher types

Prognosis

Without specific treatment

Place and time—The gross case-mortality of pneumococcal pneumonia varies greatly not only with locality but also from year to year in the same locality. In general the mortality before the introduction of specific measures of treatment was higher in the United States than in Europe; this is shown in Table VII.

TABLE VII
MORTALITY OF PNEUMOCOCCAL PNEUMONIA WITHOUT SPECIFIC TREATMENT

Place	Authors	No. of cases	Gross mortality per cent
London	Ryle and Waterfield (1922–1930) Davies, Hodgson and Whitby (1922–1931)	154	16 0
Glasgow	Cruickshank (1930–1932)	859	19 0
New York	Cecil, Baldwin and Larsen (1920–1925)	1,107	30 8
Boston	Tilghman and Finland (1929–1935)	1,306	51 4

Type of pneumococcus—The mortality varies with pneumococcal types, types II and III being in general the most fatal, the high mortality in type III pneumococcal pneumonia is probably largely due to the high incidence of this type in the older age-groups

Bacteraemia—The presence of a detectable bacteraemia indicates a more grave prognosis Cecil, Baldwin and Larsen (1927) in New York found that of patients having sterile blood cultures 18 7 per cent died, whereas of those having positive blood cultures 83 1 per cent died

Leucocyte count—The leucocyte count is of prognostic significance. A total count below 15,000 per cubic millimetre with established consolidation is unfavourable. In general the higher the leucocytosis the better the prognosis, though very high counts above 50,000 per cubic millimetre may be associated with a higher mortality

Age—The mortality varies greatly with age In infants below 2 years, it is comparable with that in adults, between the ages of 2 and 12 it is much lower, and may be no more than one-tenth of that in adults

With specific treatment

Specific therapy reduces the mortality The first specific method available was serum therapy, which, if given on the first or second day, produced some diminution in mortality Chemotherapy by sulphonamides is much simpler to administer and more effective, remaining effective late in the course of the disease; therefore it very rapidly displaced serum therapy Penicillin is also effective; no convincing differences have been demonstrated between series of cases treated with sulphonamides and with penicillin The newer antibiotics,

Specific pneumonias associated with mixed bacterial infections

The usual method of determining the aetiology of a bacterial pneumonia clinically is by the detection of organisms of known invasive power in the sputum Organisms such as streptococci of the non-haemolytic and *Str. viridans* groups, Gram-positive micrococci, *Neisseria pharyngis* and *N catarrhalis* are generally regarded as non-pathogenic, and are disregarded Even so, cases of pneumonia are not infrequent in which two potentially invasive types of bacteria are found in the sputum In these, the only ways of determining with certainty which of them is causing the pneumonia, or whether both are concerned, are (1) by investigating the bacterial flora of the pulmonary lesion itself, either by lung puncture or at necropsy, and (2) by attempting to demonstrate specific immunity reactions in the blood , (3) occasionally, also, a double infection of the blood stream is detectable

ACUTE SPECIFIC BACTERIAL PNEUMONIAS OTHER THAN PNEUMOCOCCAL

Pneumonias due to pure infections with bacteria other than pneumococci are less frequent than pneumococcal pneumonias *Streptococcus haemolyticus*, *Staphylococcus aureus*, and *Haemophilus influenzae* are found in association with pneumonias during influenza epidemics more frequently than at other times During the 1918-19 influenza pandemic, many local epidemics of secondary infections with organisms of these groups were seen It thus arises that outbreaks of pneumonia occurring at this time, in which it is highly probable that the virus played an important part, have been recorded in the literature as due to the bacterial organism which was locally prevalent Although it is difficult to differentiate clearly in such cases of mixed aetiology between the effects of the virus and of the bacterium, certain features of these cases recognizably depended upon the nature of the bacterial infection, and are similar to those seen in cases associated with the bacteria of the same group, occurring sporadically and presumably without concomitant virus infection In this section an attempt is made to describe the principal features of pure infections of the lung with various bacteria , the pneumonias associated with virus as well as bacterial infection are discussed separately In addition to the pneumonias due to those organisms which also occur as frequent associates of viruses, the characteristic pneumonias associated with Friedlander's bacillus and with the tubercle bacillus are described, and finally the pneumonic manifestations occasionally caused by certain organisms more commonly associated with acute generalized infections are mentioned

Incidence —The incidence of sporadic cases of pneumonia due to haemolytic streptococci, to staphylococci and to Friedlander's bacillus, relative to that of

consolidation The course is very variable The principle criterion, however, is the bacteriology of the sputum, which in these cases shows a mixed "*normal*" flora, in which pneumococci usually are not present at all or there may be at most a small number of pneumococci of one of the higher types

Prognosis

Without specific treatment

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[illegible] more grave [illegible] f patients [illegible] g positive blood cultures 83 [illegible] per cent.

Leucocyte count—The leucocyte count is of prog[illegible] A total count below 15,000 per cubic millimetre with established consolidation is unfavourable In general the higher the leucocytosis the better the prognosis, though very high counts above 50,000 per cubic millimetre may be associated with a [illegible]

[illegible] In infants below 2 years, it is [illegible] and

With specific treatment

Specific therapy reduces the mortality The first specific meth[illegible] ble was serum therapy, which, if given on the first or second day, produced some diminution in mortality Chemotherapy by sulphonamides is much simpler to administer and more effective, remaining effective late in the course of the disease; therefore it very rapidly displaced serum therapy Penicillin is also effective, no convincing differences have been demonstrated between series of cases treated with sulphonamides and with penicillin The newer antibiotics,

chloramphenicol and aureomycin, are no more effective than penicillin, and give rise to more undesirable side-effects (Medical Research Council, 1951); they are more difficult to administer to severely ill patients. The mortality after adequate specific treatment, although much reduced, remains variable, such factors as age, or the presence of complicating respiratory, cardiovascular or other disease, having an even greater relative effect than before such treatment was available

Specific pneumonias associated with mixed bacterial infections

The usual method of determining the aetiology of a bacterial pneumonia clinically is by the detection of organisms of known invasive power in the sputum Organisms such as streptococci of the non-haemolytic and *Str. viridans* groups, Gram-positive micrococci, *Neisseria pharyngis* and *N catarrhalis* are generally regarded as non-pathogenic, and are disregarded Even so, cases of pneumonia are not infrequent in which two potentially invasive types of bacteria are found in the sputum In these, the only ways of determining with certainty which of them is causing the pneumonia, or whether both are concerned, are (1) by investigating the bacterial flora of the pulmonary lesion itself, either by lung puncture or at necropsy, and (2) by attempting to demonstrate specific immunity reactions in the blood, (3) occasionally, also, a double infection of the blood stream is detectable

ACUTE SPECIFIC BACTERIAL PNEUMONIAS OTHER THAN PNEUMOCOCCAL

Pneumonias due to pure infections with bacteria other than pneumococci are less frequent than pneumococcal pneumonias. *Streptococcus haemolyticus*, *Staphylococcus aureus*, and *Haemophilus influenzae* are found in association with pneumonias during influenza epidemics more frequently than at other times During the 1918–19 influenza pandemic, many local epidemics of secondary infections with organisms of these groups were seen It thus arises that outbreaks of pneumonia occurring at this time, in which it is highly probable that the virus played an important part, have been recorded in the literature as due to the bacterial organism which was locally prevalent Although it is difficult to differentiate clearly in such cases of mixed aetiology between the effects of the virus and of the bacterium, certain features of these cases recognizably depended upon the nature of the bacterial infection, and are similar to those seen in cases associated with the bacteria of the same group, occurring sporadically and presumably without concomitant virus infection In this section an attempt is made to describe the principal features of pure infections of the lung with various bacteria; the pneumonias associated with virus as well as bacterial infection are discussed separately In addition to the pneumonias due to those organisms

Incidence—The incidence of sporadic cases of pneumonia due to haemolytic streptococci, to staphylococci and to Friedländer's bacillus, relative to that of

pneumococcal pneumonia may be exemplified by the figures of Humphrey, Joules and van der Walt (1948) and of Bullowa and Gleich (1938) which are quoted in the section on pneumococcal pneumonia.

Haemolytic streptococcal pneumonia

Aetiology.—Streptococci of the *alpha*-haemolytic or *Str. viridans* group are almost constant inhabitants of the upper respiratory tract, and are probably never initial invaders of the lung. *Beta*-haemolytic streptococci occur less frequently in the nasopharynx of normal persons. The most commonly occurring haemolytic streptococci in human infections, including respiratory ones, belong to Lancefield's group A.

Pneumonias due to haemolytic streptococcal infection superimposed on virus infections are probably more numerous than those in which the streptococci appear to be the primary invaders. During the 1918–19 influenza pandemic, local outbreaks of haemolytic streptococcal secondary infection occurred, producing characteristic types of lung lesions. Measles pneumonia is frequently associated with haemolytic streptococci. Haemolytic streptococci may also be prominent in some of the less well-defined local epidemics of "febrile catarrhs"; and these may be complicated by lung lesions due to haemolytic streptococci. Sporadic cases of haemolytic streptococcal pneumonia, in which there is no evidence of an epidemic virus infection, are generally associated with haemolytic streptococcal infections of the upper respiratory tract, manifested by sore throat or a definite follicular tonsillitis. The figures quoted above indicate that such sporadic cases may amount to *1* in *30* or *40* of all pneumonias.

Pathogenesis.—The frequent association of haemolytic streptococcal pneumonia with previous haemolytic streptococcal infection of the upper respiratory tract, as well as the extensive involvement of the smaller bronchi and bronchioles in the inflammatory [illegible]
are the result [illegible]
by a techniqu[illegible]
produce pneumonia consistently in monkeys by intratracheal injection of cultures of haemolytic streptococci. They produced two main types of lesion: (1) an interstitial pneumonia and (2) a confluent lobular pneumonia. These they regarded as similar to the lesions observed in haemolytic streptococcal pneumonia in man. They found that interstitial pneumonia followed injections of small amounts of culture, and was the expression of considerable resistance to the spread of the infection in the lungs, whereas a pneumonia in confluent lobular lesions followed injection of larger amounts of culture, and was the expression of lack of resistance. Study of early histological changes led them to the conclusion that the streptococci invaded the lung through the walls of the larger bronchi, thence spreading in the interstitial tissue and lymphatic vessels.

Pathology.—Accounts of the pathological changes in haemolytic streptococcal pneumonia have mostly been based on the findings in cases occurring in influenza or measles epidemics, and it is therefore uncertain whether all the features described can be attributed entirely to the haemolytic streptococcus. MacCallum (1932) described two main types of lesion. One he described as interstitial broncho-pneumonia. In this, the bronchial tree, especially in its finer divisions,

was the seat of gross inflammatory changes, with epithelial destruction in the bronchioles; around the bronchioles there was some haemorrhage, and later a dense fibrinous exudate with a few leucocytes and lymphocytes appeared in the peribronchiolar alveoli The alveolar walls, and the interstitial tissue generally, showed remarkable thickening and infiltration with mononuclear cells, this interstitial infiltration and the alveolar exudate tended to become organized In addition, pleural involvement occurred early and often gave rise to large pleural effusions, which might remain clear or merely turbid for a long time These changes, in the interstitial tissue especially, are similar to those described in association with pure virus infections in animals, and other organisms as well as streptococci were sometimes found in association with them In the second type of lesion described by MacCallum there was little involvement of the interstitial tissue The principal changes were patchy areas of soft haemorrhagic consolidation, which might coalesce, with enormous numbers of streptococci in the exudate, as if no resistance were being offered to the spread of the infection through the lung.

Clinical picture.—In cases not associated with virus influenza or measles, there is usually a preceding sore throat or follicular tonsillitis The development of pneumonic symptoms is usually insidious Increased prostration, cough, high fever and tachypnoea, with perhaps indefinite chilly sensations, are the most frequent symptoms at the onset The sputum is often thin, muco-purulent and blood-stained, containing large numbers of haemolytic streptococci. When the disease is fully developed, the illness is, on the average, more severe than pneumococcal pneumonia. Very high fever with delirium and well-marked cyanosis are usual Pleurisy, followed by massive effusion, may occur. The physical signs are very variable On account of the patchy distribution of the lesions, signs of consolidation may not be detectable Impairment of percussion note over the most affected areas, usually at one or both bases, weak breath sounds and medium to coarse râles are the most usual signs When a massive pleural effusion is present, the appropriate signs are to be found, but paracentesis is often required to detect smaller effusions with certainty.

Complications.—In the 126 cases in the series of Bullowa and Gleich (1938), *bacteraemia* occurred in 27 (23 3 per cent), the mortality of these was 88 9 per cent The gravity of blood invasion is thus greater than is the case with pneumococcal pneumonias Empyema is a very common complication, occurring in about 50 per cent of cases The fluid is generally not purulent at first and appears as a turbid effusion in a free pleural space Inflammations of other serous membranes may occur but are relatively rare *Pulmonary fibrosis* is a possible late complication, as might be expected from the severe reaction in the interstitial tissues in the acute stage

Mortality.—In the series of Bullowa and Gleich (1938) the gross mortality rate was 32 8 per cent [illegible]
in a series of 346 cases [illegible]
during the 1918–19 infl[illegible]
can certainly be much reduced by specific treatment.

Treatment.—Since *Str haemolyticus* is sensitive to both sulphonamides and

type in new-born infants and in young infants has been described In the series of Bullowa and Gleich (1938), staphylococci were the cause of 0·7 per cent of pneumonias in adults, and of 2 5 per cent in infants (Table II)

In staphylococcal pyaemia.—Staphylococcal pneumonia may also arise as part of a staphylococcal pyaemia, when it is accompanied by such other localizations as osteomyelitis, arthritis and perinephric abscess. Multiple metastatic staphylococcus-infected infarcts of the lung, leading to abscess formation, may also occur in staphylococcal pyaemia. In this latter group of cases, it is usually obvious that the lung lesions are secondary to an antecedent lesion elsewhere; when a localized staphylococcal pneumonia is accompanied by staphylococcal lesions in other organs, it may be uncertain which is the primary focus of infection.

Pathology

The most prominent feature is the tendency to suppuration. According to Reimann (1938), localized areas of intense bronchitis and bronchiolitis are seen, with pulmonary lesions grouped around them These areas may be lobar in extent, or there may be scattered small well-defined areas of haemorrhagic consolidation There is frequently pleural exudation of turbid fluid containing staphylococci. In later cases, foci of suppuration, grouped around the bronchioles and involving them, break down into miliary abscesses, which may coalesce, giving rise to gross abscess cavities Ulceration of an abscess into the pleura may lead to pyopneumothorax with pleuro-bronchial fistula Microscopically, the interlobular septa, lymphatic vessels and interstitial tissues are infiltrated with polymorphonuclear leucocytes Enormous numbers of staphylococci may be seen in the affected areas In cases which are primarily bronchogenic, late metastatic lesions in other organs are, surprisingly, not common.

Clinical picture

Symptoms—In adults, the disease follows a variable course There is often a preceding infection of the upper respiratory tract. The onset of pneumonic symptoms is usually insidious, but the patient rapidly becomes severely ill, with great prostration, dyspnoea, cyanosis, cough and expectoration Sometimes the onset is more sudden, with a rigor or pleuritic pain The sputum is variable in quantity, but it is usually purulent and sometimes pink with blood, or blood-streaked; in typical cases it contains enormous numbers of staphylococci Fever is usually swinging in type, and may be accompanied by recurrent rigors and severe sweats In fulminating cases, death ensues within a few days. In less severe cases, the swinging temperature persists and, with the formation of abscesses in the consolidated areas, the purulent expectoration becomes more copious. In the absence of specific treatment, defervescence in favourable cases is very gradual; relapses may occur, with appearance of new lesions in previously unaffected parts of the lung Empyema or pyopneumothorax often accompanies the acuter phase of the pneumonia.

Signs.—Radiographically, the early changes consist of localized areas of opacity in any part of the lung field. These may increase to occupy whole lobes Later in the disease, areas of softening and cavitation, giving rise to rather characteristic cyst-like appearances, may develop in some of the affected areas; in spite of

this, complete restoration to normal is possible These rather characteristic staphylococcal lung abscesses have been well described by Brock (1945)

Prognosis

The gross mortality in untreated cases is high. In Bullowa's series (Table II), 54 2 per cent of the adults with staphylococcal pneumonia died (Bullowa and Gleich, 1938) The prognosis has been greatly improved by adequate penicillin treatment.

Staphylococcal pneumonia in infants

Staphylococcal pneumonia is relatively more frequent in infants under 1 year of age, including the new-born, than in older age-groups The pathological features of the disease are similar to those observed in adults: turbid staphylococcus-infected pleural effusion is especially frequent, as is abscess formation in the lung, leading to perforation of the pleura and pyopneumothorax The latter event may give rise to the clinical picture of a tension spontaneous pneumothorax This event early in the disease, together with the thin-walled abscesses, which may appear later and may become distended into thin-walled cystic spaces, sometimes of great size, frequently give rise to diagnostic difficulty. The differential diagnosis of bronchogenic staphylococcal pneumonia from pyaemic staphylococcal lesions of the lung, secondary to staphylococcal sepsis elsewhere (especially infections of the umbilical cord in new-born infants and osteomyelitis in older infants), may be difficult The mortality of primary staphylococcal pneumonia in infants is high (probably from 60 to 70 per cent) without specific treatment, but it can be reduced by the proper use of antibiotics

Treatment

Staphylococcal pneumonia should be treated in the first instance with penicillin Full doses, of the order of 1,000,000 units a day for an adult, should be used at first This may with advantage be combined with standard dosage of a suitable sulphonamide sulphadimethylpyrimidine (Sulphamezathine) is recommended If suppuration occurs in the pneumonic lung, antibiotic treatment should be continued; staphylococcal abscesses usually heal under such treatment, although a thin-walled cyst-like cavity may persist, without symptoms, for a long time at the site of the abscess It is essential, however, to estimate the sensitivity of the infecting staphylococcus to penicillin and to other antibiotics If the staphylococcus is resistant to penicillin, aureomycin, in doses of 1 gramme 4 times daily initially, reduced to 0 5 gramme 4 times daily after defervescence, is the drug of choice A close watch should be kept for the development of pyothorax, if this develops it should be treated initially by aspiration and the intrapleural injection of penicillin

Haemophilus influenzae pneumonia

Bacteriology

It is unfortunate that the small Gram-negative bacillus, first isolated by Pfeiffer and regarded by him as the cause of influenza, has continued to be known by a name which suggests a relation to this disease *Haemophilus influenzae* certainly

is not the primary cause of influenza, even though it is sometimes found in association with the pulmonary lesions of influenza. Its exact role in respiratory infections is difficult to estimate. It may be part of the flora of the upper respiratory tracts of normal persons. Some strains, at least, are independently pathogenic, and can cause meningitis, endocarditis or septicaemia. Blake and Cecil (1920) were able to produce pneumonia in monkeys by intratracheal injection of Pfeiffer's bacillus, but in man pneumonia due to a pure infection with this organism, apart from an associated virus infection, is extremely rare. On the other hand, Pfeiffer's bacillus may be found as part of the bacterial flora in mixed-infection pneumonias, in most of the recorded cases in which it has been found in pneumonic lungs in inter-epidemic times, and in a large proportion of those observed at the times of influenza epidemics, other pathogenic organisms, especially pneumococci, have accompanied it. The association of Pfeiffer's bacillus with pneumococci in the 1917 epidemic of purulent bronchitis (*see* page 50) is of interest, especially in relation to the pathological changes associated with Pfeiffer's bacillus pneumonia.

Pathology

Brannan and Goodpasture (1924) described the characteristic appearances of Pfeiffer's bacillus pneumonia during an inter-epidemic period, on the basis of 5 cases coming to necropsy, 4 of which showed a mixed infection, generally with pneumococci. The cut surface of the lungs showed grey peribronchiolar areas of consolidation, the bronchiole in the centre being distended with yellow pus. The smaller bronchi were similarly the seat of a purulent bronchitis. The intervening alveoli were filled with sero-purulent or haemorrhagic exudate. The purulent exudate in the bronchioles contained large numbers of small Gram-negative bacilli. Microscopically, the lumina of the bronchioles were dilated and contained many polymorphonuclear leucocytes; the bronchial and bronchiolar walls showed inflammatory thickening and even some ulceration. The alveoli around the involved bronchioles were filled with fibrinous plugs, containing few cells; those more peripherally placed contained a polymorphonuclear-cell exudate with little fibrin. In intervening alveoli, haemorrhage or focal areas of necrosis might be seen. Pleural involvement was not prominent. The larger bronchi showed some inflammation, but were not so severely affected as the smaller air-tubes. These changes were similar in several respects to those observed in association with Pfeiffer's bacillus invasion of the lungs during the influenza pandemic; but pulmonary oedema, dilatation of the alveolar ducts, and the interstitial tissue reaction observed in association with virus diseases were not present.

Clinical picture, diagnosis and treatment

Clinical aspects.—There is no clearly distinctive clinical feature by which a pneumonia may be suspected to be due to Pfeiffer's bacillus. The course is atypical, and sometimes prolonged, symptoms of a purulent bronchitis may be present. The physical signs are usually those of widespread patchy lobular consolidation, which may become confluent at a late stage.

Diagnosis.—Diagnosis during life depends upon the finding of *H. influenzae*

predominating in the sputum, in order to establish that this organism is the causative agent, it should also be shown to be present in the lung at necropsy, or else by lung-suction, and studies to exclude a virus infection are desirable. The question is one of mainly academic interest

Treatment.—In treatment, if it is suspected that *H. influenzae* is prominent in the causation of a pneumonia, it would be reasonable to use aureomycin, in the dosage recommended above for the treatment of penicillin-resistant staphylococcal pneumonia, combined with Sulphamezathine in standard dosage.

RARE FORMS OF ACUTE SPECIFIC BACTERIAL PNEUMONIA

The pneumonias mentioned in this section are rare manifestations of bacterial infections which commonly give rise to more generalized diseases; for this reason, brief reference only is made to them.

Bacillus anthracis pneumonia

Broncho-pulmonary anthrax, or wool-sorter's disease, is the rarest of the forms of anthrax It occurs in men who handle raw wool or hides infected with anthrax, the bacilli gaining access to the body by inhalation of the infected dust. In the common form of anthrax, the organisms enter by the skin, causing a malignant pustule, from which they enter the blood stream, causing a septicaemia The pulmonary form is characterized at the onset by a severe bronchitis, and the progress of the illness is rapid, with dyspnoea, cyanosis, and blood-stained expectoration A patchy pneumonia develops. Pathologically, there is an intense bronchitis, with haemorrhagic exudate and sometimes ulceration, there is also a patchy haemorrhagic consolidation of the lung, which may progress to suppuration in places The prognosis without specific treatment is very grave, nearly all the patients dying within a few days of the onset of acute symptoms Diagnosis depends upon the history of exposure to possibly infected dust, and upon the finding of *B. anthracis* in sputum or blood culture Prophylactic measures to protect workers in raw wool, fur and hides from dust have rendered the disease extremely rare *In vitro*, the anthrax bacillus is sensitive to penicillin, streptomycin and aureomycin, but there is no record of the use of any of these antibiotics in broncho-pulmonary anthrax, it would be reasonable to attempt treatment with very large doses of penicillin, say 2,000,000–4,000,000 units daily in the first instance

Pasteurella pestis pneumonia

Aetiology—The pneumonic form is one of the rarer varieties of plague It is of particular importance, however, because it can be transmitted directly from person to person by droplet infection, in contrast with the bubonic and septicaemic forms in which the infection is transmitted by fleas from infected rats In epidemics of pneumonic plague, the infection is presumably derived at first from rats in the usual way, a specific pneumonia develops in one or several cases, and from these direct case-to-case infection by droplet infection starts The spread of the infection is more rapid in pneumonic than in bubonic outbreaks, but pneumonic outbreaks generally remain strictly localized It is doubtful whether pneumonic plague is as intensely contagious as was once thought. Cold

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damp climatic conditions favour, while hot dry conditions hinder, the spread of pneumonic plague The largest recorded outbreaks have been in Manchuria; small localized outbreaks are recorded in areas in which bubonic plague is endemic A small outbreak occurred in East Suffolk in 1910, and one or two other similar small outbreaks of fatal pneumonic illnesses in the same area, in the few years preceding that date, seem likely to have been due to the same cause (Bulstrode, 1911)

Pathology and clinical features.—Pathologically, the pneumonia of plague consists of a patchy soft oedematous haemorrhagic consolidation, with multiple sub-pleural ecchymoses, severe bronchitis and much swelling of the broncho-pulmonary glands The onset of illness is sudden, with severe constitutional symptoms, prostration, headache, vomiting, diarrhoea, drowsiness and delirium are common, cough, with sputum (which tends to be frankly blood-stained), dyspnoea and cyanosis follow In the absence of specific treatment, the disease is nearly always fatal within 4 days

Diagnosis—Diagnosis during an epidemic of bubonic plague is simple; when bubonic cases have not been recognized, the outbreak may present as a rapidly developing epidemic of uniformly fatal primary pneumonia, which should immediately cause suspicion of pneumonic plague. A concurrent epizootic,

Treatment—Elaborate isolation of patients is, of course, essential Details of prophylactic measures belong rather to general discussions of plague than to the present context In therapy, streptomycin in large doses (4–6 grammes daily at first), combined with full doses of a suitable sulphonamide (sulphadimethyl-pyrimidine, Sulphamezathine) should be used.

Tularaemic pneumonia

Bacteriology—Pneumonia is one of the possible manifestations of tularaemia; this disease is caused by a minute Gram-negative bacillus, which has been named *Pasteurella tularensis* (or *Brucella tularensis*) It has been reported to be endemic among small rodents in certain parts of the United States of America, Japan, Siberia, Norway, Sweden and Czechoslovakia Tularaemia has not been recorded in Great Britain except as the result of an accidental infection of laboratory workers.

Clinical features—In about 50 per cent of cases, some evidence of pulmonary involvement may be obtained, but a small proportion present primarily in a pneumonic form The pneumonia has been described as characterized by nodules of hepatization, in which central areas of coagulation necrosis may occur. *Past tularensis* may be cultivated from the lesions Diagnosis depends upon the isolation of the causative organism from sputum or blood, or upon a rising titre of agglutinins in the serum

Prognosis—Without specific treatment, the mortality is high. Streptomycin, aureomycin and chloramphenicol appear to be effective therapeutically.

Other bacterial diseases in which pneumonia may occur

Enteric fevers.—In enteric fevers, a bronchitis occasionally occurs at the onset.

Pneumonia may develop, especially in the later stages of fatal cases, but it appears to be most commonly due to other organisms than those of the enteric group, often to pneumococci Occasionally, cases have been recorded in which organisms of the enteric group have been found predominating in sputum cultures, or in pneumonic lungs examined at necropsy Apparently, no clinical distinction can be made in enteric fevers between the common non-specific pneumonias and the very rare pneumonias due to the causative organism of the primary disease

Undulant fever—In undulant fever, pneumonias may occur, either as an incident during the course of the disease or as one of the phenomena of the terminal stage These pneumonias are almost invariably not associated with brucella infection of the lungs themselves, according to Reimann (1938), only one authentic case of pneumonia in which brucellae have been found in the lungs at necropsy has been recorded

ACUTE TUBERCULOUS PNEUMONIAS

Three types of tuberculous lung disease may present clinically as pneumonias. (1) "epituberculosis", (2) tuberculous lobar pneumonia, and (3) tuberculous broncho-pneumonia

"Epituberculosis"

Pathogenesis

This title, first used by Eliasberg and Neuland in 1920, describes a group of cases in children and infants, characterized by a prolonged illness of varying severity, with cough, a variable degree of fever, and radiographic and sometimes clinical signs of pulmonary consolidation, affecting any part of the lung, but more often the upper lobes or the middle lobe Evidence of a relation to tuberculosis is given (1) by a strongly positive dermal tuberculin reaction, and usually by a positive history of contact within the family with open tuberculosis, (2) by radiographic evidence of enlargement of hilar lymph-nodes in association with the consolidated segment or lobes, (3) in some cases by the detection of tubercle bacilli in the resting gastric contents

Clinical picture and course

The onset of the illness is usually insidious, with cough, loss of weight, some dyspnoea, and occasionally pain in the chest The severity of the symptoms is very variable Occasionally, symptoms are very slight, more rarely there may be a more acute onset, simulating that of an acute pneumonia The course is always prolonged On examination, signs of established consolidation in any part of the lung may be found, or physical signs may be less definite, with only some impairment of percussion note, weak breath sounds, and a few râles over the affected part of the lung Radiography shows homogeneous shadows, extending out from the hilum into the affected lobe, they may involve part of the lobe or a whole lobe

After a prolonged course, resolution is usually complete, but there may remain small dense shadows, indicative of calcified pulmonary and lymph-node lesions in the previously affected area

Morbid anatomy

Since the group has been defined largely by the clinical criterion of a benign course, doubt is likely to be cast upon the validity of including in it any case that terminates fatally Hence there has been much discussion of the nature of the lesion in the lungs in these cases, especially whether it is to be regarded as an atelectasis due to pressure on segmental or lobar bronchi by enlarged tuberculous lymph-nodes, or as a benign variety of tuberculous pneumonia Bronchoscopic studies have shown that distortion or occlusion of bronchi, or even ulceration of enlarged lymph-nodes into them, may be present On the other hand, the few pathological studies which have been made (Reichle, 1933; Fish, 1937; Fish and Pagel, 1938) have shown a pneumonic condition of the lung with very few tubercle bacilli present A reasonable hypothesis, covering both these observations and the clinical facts, is that "epituberculosis" of all types is due to the effects of enlarged lymph-nodes on bronchi at one end of the scale is a pure atelectasis, caused by occlusion due to simple pressure from without, and at the other a pneumonic reaction, set up by leakage of caseous material containing tuberculo-protein and a few bacilli from an ulcerated node into the segment or lobe; all types of intermediate reactions may occur

Diagnosis

Radiographic and laboratory methods.—Atelectasis, due to pressure by tuberculous glands, gives rise to the usual clinical and radiographic evidences of atelectasis, and investigation of the bronchial tree—preferably by bronchoscopy, or alternatively by bronchography—will demonstrate bronchial obstruction. A benign tuberculous pneumonia may be suspected in a child who has a prolonged pulmonary consolidation (lobar or partial-lobar in extent), with a strongly positive Mantoux reaction and, perhaps, a history of close contact with open tuberculosis; the diagnosis is made more certain by the finding of tubercle bacilli in stomach contents and washings

Differential diagnosis—The differential diagnosis from progressive pneumonic tuberculosis can be made with certainty only by observing the course, although frequently the mildness of the symptoms may suggest, even at the onset, the relatively benign nature of the lesion, a similar suggestion is given by the more uniform and less dense opacity of the radiographic shadows, and their tendency to spread out fan-wise from the hilum, and by the strongly positive Mantoux reaction Occasionally, "epituberculosis" may be confused with bacterial or other acute non-tuberculous pneumonias In general, the child with even the acuter types of "epituberculosis" is not so acutely ill as would be expected with an acute non-tuberculous pneumonia The points mentioned above will be helpful, but often a period of observation is required to establish the diagnosis.

Treatment

The treatment of all types of "epituberculosis" consists initially of rest in bed, combined with careful clinical and radiographic supervision Most cases, especially of the atelectatic variety, respond well to such treatment; indications for the use of streptomycin are discussed elsewhere.

Tuberculous lobar pneumonia

(*Synonyms*: caseous pneumonia, acute lobar pneumonic phthisis.)

Tuberculous lobar consolidation is occasionally the first clinical manifestation of pulmonary tuberculosis, either in adults or in children A lobar consolidation of tuberculous origin may rarely appear during the course of established pulmonary tuberculosis, usually as a result of bronchogenic spread after a haemoptysis, an operation, or an intercurrent acute respiratory infection The term, tuberculous lobar pneumonia, should be recognized as a convenient name for a group characterized by the presence at one stage of uniform consolidation throughout a lobe, caused by an exudative reaction to the tubercle bacillus, and somewhat arbitrarily selected for consideration from an uninterrupted series of types of pulmonary tuberculosis The group ranges from cases with an acute onset simulating that of a non-tuberculous acute pneumonia, to others with an insidious onset resembling that usually associated with pulmonary tuberculosis; and from those considered in the previous section, the course of which is relatively benign, showing a tendency to resolution, to those showing rapid caseation and cavitation, leading to death within a few weeks or months

Pathology

The factors which determine the occurrence of a tuberculous lobar pneumonia are obscure It is probable that a lobar exudative reaction can occur only in a person who has been rendered highly allergic by previous primary infection Although it seems likely that the seeding of a whole lobe with tubercle bacilli is usually the consequence of rupture of a caseous focus in the lung or in a lymph-node into the tracheo-bronchial tree, evidence of such an event may not be obtainable

Any lobe or lobes may be involved in a tuberculous pneumonia. The consolidation at first has a peculiar translucent grey or pinkish-grey colour, with a smooth cut surface covered with viscid exudate, this stage has been called gelatinous pneumonia Microscopically, the alveoli are filled with exudate, containing many macrophages and a smaller number of polymorphonuclear cells and lymphocytes; a varying number of giant-cell systems are scattered through the affected area At this stage, resolution, even as far as complete restoration to normal, may occur; the benign tuberculous pneumonias discussed in the preceding section progress no further than this

In the less favourable cases, the consolidation becomes dryer and yellow in colour, and eventually areas of caseation appear; microscopically, the alveolar exudate becomes more fibrinous, the cells both of the exudate and of the lung tissue degenerate, areas of necrosis and liquefaction develop, and around them polymorphonuclear leucocytic infiltration appears Thus, cavities lined by caseous walls are formed A varying amount of fibrous-tissue reaction may occur, tending to limit the progress of the disease, and converting it into the fibro-caseous form of the disease, but in many cases of caseous pneumonia, especially if uncontrolled by antibacterial therapy, the breaking down of the caseous areas into cavities leads to spread of the disease by aspiration into multiple lobular foci scattered throughout the lungs, with an early fatal outcome.

Morbid anatomy

Since the group has been defined largely by the clinical criterion of a benign course, doubt is likely to be cast upon the validity of including in it any case that terminates fatally Hence there has been much discussion of the nature of the lesion in the lungs in these cases, especially whether it is to be regarded as an atelectasis due to pressure on segmental or lobar bronchi by enlarged tuberculous lymph-nodes, or as a benign variety of tuberculous pneumonia. Bronchoscopic studies have shown that distortion or occlusion of bronchi, or even ulceration of enlarged lymph-nodes into them, may be present On the other hand, the few pathological studies which have been made (Reichle, 1933; Fish, 1937; Fish and Pagel, 1938) have shown a pneumonic condition of the lung with very few tubercle bacilli present. A reasonable hypothesis, covering both these observations and the clinical facts, is that "epituberculosis" of all types is due to the effects of enlarged lymph-nodes on bronchi. at one end of the scale is a pure atelectasis, caused by occlusion due to simple pressure from without, and at the other a pneumonic reaction, set up by leakage of caseous material containing tuberculo-protein and a few bacilli from an ulcerated node into the segment or lobe; all types of intermediate reactions may occur

Diagnosis

Radiographic and laboratory methods—Atelectasis, due to pressure by tuberculous glands, gives rise to the usual clinical and radiographic evidences of atelectasis, and investigation of the bronchial tree—preferably by bronchoscopy, or alternatively by bronchography—will demonstrate bronchial obstruction. A benign tuberculous pneumonia may be suspected in a child who has a prolonged pulmonary consolidation (lobar or partial-lobar in extent), with a strongly positive Mantoux reaction and, perhaps, a history of close contact with open tuberculosis; the diagnosis is made more certain by the finding of tubercle bacilli in stomach contents and washings

Differential diagnosis—The differential diagnosis from progressive pneumonic tuberculosis can be made with certainty only by observing the course, although frequently the mildness of the symptoms may suggest, even at the onset, the relatively benign nature of the lesion, a similar suggestion is given by the more uniform and less dense opacity of the radiographic shadows, and their tendency to spread out fan-wise from the hilum, and by the strongly positive Mantoux reaction Occasionally, "epituberculosis" may be confused with bacterial or other acute non-tuberculous pneumonias In general, the child with even the acuter types of "epituberculosis" is not so acutely ill as would be expected with an acute non-tuberculous pneumonia The points mentioned above will be helpful, but often a period of observation is required to establish the diagnosis.

Treatment

The treatment of all types of "epituberculosis" consists initially of rest in bed, combined with careful clinical and radiographic supervision. Most cases, especially of the atelectatic variety, respond well to such treatment; indications for the use of streptomycin are discussed elsewhere

pulmonary or less commonly in lymph-nodes) into previously unaffected parts of the lungs.

Clinical picture

In the cases in which tuberculous broncho-pneumonia is the earliest detected lesion, the onset is usually insidious, but an intercurrent catarrhal infection may cause an aggravation of symptoms, which induces the patient to seek medical advice for the first time, and may lead to a provisional diagnosis of "pneumonia". The principal symptoms are irregular swinging pyrexia, cough and sputum, dyspnoea, and sometimes sweating, haemoptysis or pain in the chest In severe cases, there may be great dyspnoea and cyanosis, wasting is generally rapid, and the patient may lapse into a cachectic state with fatal termination within a few months

Differential diagnosis

In these cases, there may be difficulty during the earlier stages in differential diagnosis from non-tuberculous lobular pneumonia, either of the acute specific varieties or of the less specific aspiration variety after catarrhal infections; bacteriological examination of the sputum should settle the diagnosis, for in tuberculous broncho-pneumonia there is rarely difficulty in demonstrating the bacillus in the sputum

Diagnosis

When tuberculous lobular pneumonia arises in the course of chronic pulmonary tuberculosis, the diagnosis is usually easy, but occasionally, especially after general anaesthesia or a catarrhal infection, a lobular pneumonia, the aetiology of which is doubtful, may appear in a patient with known chronic pulmonary tuberculosis In such cases, the course of the disease, best followed by serial radiography, is the only feature by which diagnosis can be made with certainty since tubercle bacilli, if present in the sputum, may have come from the old lesions, if the new lesion clears rapidly after treatment with sulphonamides and penicillin, it is probably a non-tuberculous lobular pneumonia

The radiographic changes of tuberculous lobular pneumonia are similar to those of other [illegible]
culous lesions [illegible]
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ERRATUM

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Chapter 21 *read* Chapter 16.

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EUMONIA

. complication of epidemic influenza and is the cause of the high mortality of influenza pandemics.

Clinical types

The clinical picture of influenzal pneumonia is very variable. Two main groups

Clinical aspects

The symptoms may develop insidiously, or there may be a sudden onset simulating that of an acute non-tuberculous pneumonia In many cases, a history of preceding vague ill-health, lassitude and loss of weight may be obtained The symptoms of the established disease are often at first confusingly similar to those of an acute non-tuberculous pneumonia, and this may be the first diagnosis made. Instead of the cyanotic flush seen in young patients with pneumococcal pneumonia, there may be pallor The sputum is less often " rusty ", and more often mucopurulent and streaked with frank blood, haemoptysis may rarely be severe. Symptoms suggestive of tuberculosis may not appear for 2 or 3 weeks; the pyrexia is maintained, there may be severe sweating, wasting and anaemia are progressive, sputum may increase in amount and become purulent, but often remains scanty, the differential diagnosis has to be made between (1) pneumococcal pneumonia, complicated by empyema or some other suppurative complication, or by delayed resolution, (2) tuberculous pneumonia, (3) other types of acute bacterial pneumonia, (4) suppurative pneumonia (pulmonary abscess), (5) a bronchial foreign body, (6) carcinoma, and (7) rarer conditions such as actinomycosis

Diagnosis

The diagnosis of tuberculous pneumonia rests eventually upon the results of bacteriological examination Although in most cases bacilli appear in the sputum or gastric contents quite soon after the onset, in a few the appearance of bacilli may be delayed for as long as 10 weeks or even more Small clear pleural effusions may develop around the affected lung, and bacilli may be found in this fluid before they appear in the sputum Physical examination at the earlier part of the illness will not distinguish the disease from lobar pneumonia due to any other organism; but râles may be more numerous and coarser, and the upper lobes are more frequently affected than in pneumococcal pneumonia.

The radiographic shadow of a tuberculous lobar consolidation during the earlier stages is exactly similar to that of a pneumococcal one, but in some cases mottling, suggestive of tuberculous infiltration, may be seen in other parts of the lung fields. Later, multiple areas of cavitation in the consolidated lobe appear, and often areas of tuberculous " infiltration " or lobular consolidation appear in the rest of the lung fields

Tuberculous broncho-pneumonia

In this type of acute pulmonary tuberculosis, there are scattered lobular pneumonic lesions, showing similar gross and microscopic characteristics and modes of progression to those of the lobar lesions of tuberculous lobar pneumonia In children and adolescents, diffuse lobular pneumonia may be the first clinically detected lesion of pulmonary tuberculosis, usually because premonitory symptoms have been unnoticed or ignored In adults, tuberculous broncho-pneumonia is usually a consequence of chronic pulmonary tuberculosis, often precipitated by haemoptysis, general anaesthesia or an intercurrent infection In either case the pneumonia is due to aspiration of infective material from older foci (either

epidemics, but the case-mortality of true influenzal pneumonia seems to be about the same in pandemics and epidemics No information is yet available about the effect of antibiotics active against the bacterial invaders on the mortality, and no antibiotic at present available has a proved action against the influenza virus.

Bacteriology

In ferrets and mice the influenza viruses alone can cause pneumonia In man, bacteria of various sorts are nearly always found in the lungs in fatal cases of influenzal pneumonia The virus is likely to be isolated from the lungs only in the case of patients dying early in the disease, usually with the "fulminating" type of pneumonia, isolation is much less frequent if the patient dies later in the illness. The type of pneumonia can be correlated to some extent with the bacteria present; pneumococci tend to be associated with lesions of lobar distribution, haemolytic streptococci with a severe diffuse lobular pneumonia and a high incidence of pyothorax, and *Haemophilus influenzae* with purulent bronchitis and patchy basal pneumonia Several types of individually virulent organisms have been found in fulminating cases but certainly in inter-pandemic epidemics, *Staphylococcus aureus*, usually in very great numbers, is the most frequent

In the 1918–19 pandemic, the type of pneumonia found in various localities varied with the locally prevalent bacteria, and local epidemics of secondary infection by a locally prevalent organism were reported.

All these observations make it likely that the pneumonias associated with influenza are due to the combined actions of the virus and of a variety of bacteria. In the fulminating cases, extensive and severe damage to the respiratory epithelium by the virus is accompanied by simultaneous invasion by strongly pathogenic bacteria In the usual type of influenzal pneumonia, virus damage of varying extents paves the way for invasion at various stages by bacteria of varying types The great number of variable factors accounts for the confusing variety of clinical pictures.

Pathology

It will be clear from the above description of the clinical aspects that the gross morbid anatomical changes in influenzal pneumonia are very varied Certain histological features, however, are commonly found Of these, the most frequent are the following (1) desquamation and necrosis of bronchial and bronchiolar epithelium; (2) cellular exudation into the interstitial tissue, (3) formation of a layer of hyaline material in the inner aspects of dilated alveolar ducts; (4) focal necrosis of alveolar walls with thrombosis of capillaries and intra-alveolar haemorrhage These changes are combined in varying degrees with those associated with bacterial pneumonias of varying sorts In the acute fulminating pneumonias, soft, intensely haemorrhagic consolidation, usually of confluent lobular distribution, is commonly seen with the naked eye; histologically, necrosis of bronchial epithelium, and of bronchiolar and alveolar walls, and intra-alveolar haemorrhage are prominent

Diagnosis

In practice, the diagnosis of influenzal pneumonia depends usually upon the knowledge that influenza is prevalent. In the usual pneumonic cases, with

can be distinguished In the first, the symptoms and signs of the pneumonia appear after an interval of usually 4 or 5 days from the onset of the influenza. The second is fortunately rare except in pandemics, and consists of cases of "fulminating" influenzal pneumonia, in which the symptoms become progressively more severe from the onset of the influenza and death results in most cases within 3 days

Pneumonia ensuing after the development of influenza

The first group includes the large majority of cases. About 4 or 5 days, but occasionally longer, after the onset of the influenza, and often at a time when the patient is beginning to feel better and may even have started getting up out of bed, there is a return of the fever and constitutional symptoms ; this may be preceded by pleuritic pain or shivering, and is followed by increased cough, expectoration and dyspnoea Clinically, many patients show a characteristic appearance apathetic and with tachypnoea, rather than distressed, alert and dyspnoeic like the patient with pneumococcal pneumonia A combination of cyanosis and pallor causes the so-called "lilac cyanosis", which tends to appear earlier than does the flushed cyanosis of pneumococcal pneumonia The pyrexia in many cases bears no relation to the severity of the illness The leucocyte count, which is usually low or normal in uncomplicated influenza, generally rises, with an increase in neutrophil percentage

The anatomical distribution and course of the pneumonia are very variable. There may be (1) patchy bilateral lobular lesions, usually basal, (2) patchy lesions at one base with massive lobar consolidation in the other lung, or (3) lobar consolidation alone The physical signs vary according to the distribution of the lesions. The scattered basal lobular pneumonias, or broncho-pneumonias, give rise to impairment of percussion note, weak breath sounds and râles, but rarely to bronchial breath sounds The physical signs of the lobar consolidations often differ from those found in pneumococcal lobar pneumonias , dullness to percussion may be extreme, and breath sounds may be weak, vesicular or even absent, instead of bronchial, so that the signs simulate those of effusion into the pleura Resolution of consolidated lobes presenting these signs is generally very slow , but the consolidated lobe may present the more usual physical signs and these less massive lesions usually resolve without undue delay

Fulminating influenzal pneumonia

In the fulminating cases, the patient is taken ill with severe influenza, and becomes steadily more prostrated, dyspnoeic and cyanosed The lilac cyanosis, caused by a combination of arterial anoxia with pallor of the skin due to a shock-like state, develops early The physical signs in the chest are variable from case to case, but generally consist in impairment of percussion note, weak breath sounds, and râles spreading upwards from both bases Most patients who present this picture die within 3 or 4 days of the onset of the "influenzal" symptoms

Mortality

The over-all mortality varies from about 25 to 40 per cent In pandemics of influenza, the incidence of pneumonia is much higher than in inter-pandemic

incidence and severity upon the associated bacterial infection Recovery is often slow, and resolution may be incomplete, leaving some residual fibrosis and possibly bronchiectasis

Pathology

The larynx, trachea and bronchi show inflammatory changes of varying severity, sharing in the general involvement of the respiratory mucosa which is a leading feature of measles The pneumonia is usually of broncho-pneumonic distribution, and its character is dependent partly upon the bacteria present There is an inflammatory reaction in the interstitial tissue, with mononuclear cells, lymphocytes and plasma cells Characteristically, the exudate in consolidated alveoli is mononuclear in type, but bacterial invasion may modify this Bacteriologically, haemolytic streptococci are often predominant, as in the United States Army epidemic of 1918 , pneumococci, *Haemophilus influenzae* and staphylococci may also be found, and the bacterial flora may be mixed

Treatment

In treatment, penicillin or one of the other wide-range antibiotics should be given from the time that the onset of pneumonia is suspected, even if, in a severe case of measles, it has not been given prophylactically Thereafter, treatment should ideally be guided by the results of bacteriological studies

PNEUMONIAS CAUSED BY VIRUSES OF THE PSITTACOSIS GROUP

Psittacosis

Epidemiology

Psittacosis, according to the original descriptions, is a disease transmitted to man from birds of the parrot family, and is characterized clinically by a severe febrile illness with predominantly constitutional symptoms at the onset, a later development of pneumonic changes in the lungs, and a high mortality Outbreaks were described in many parts of the world among persons in contact with parrots and budgerigars The disease was particularly widespread in 1929–30, when the causative virus was first identified The virus is of large particle size, and is a member of a group of viruses which includes that of lymphogranuloma venereum , it also includes a number of viruses causing pneumonia in laboratory and other animals These viruses characteristically give rise to basophilic inclusion bodies in infected cells They appear to be intermediate in many respects between rickettsiae and true viruses

In the 1929–30 epidemics, it was noted that the appearance of the human disease was often preceded by an epizootic outbreak among parrots The virus is excreted in the droppings and nasal secretions of infected parrots, and infection could often be traced to contact with such birds The virus can be carried by apparently healthy birds Rare instances of spread of infection from human cases of psittacosis to their attendants are recorded

Clinical picture

The incubation period is from 6 to 15 days The onset of the disease is sudden with rigors and sometimes vomiting Headache is severe Epistaxis

onset of pneumonia about the fourth or fifth day of the influenza, the virus is unlikely to be isolated from throat and nose washings by the time that the consolidation is established It can usually be recovered from the lungs of patients dying from fulminating pneumonia, but rarely from the lungs in fatal cases of the type of pneumonia developing later in the disease. The most generally practicable method of determining whether or not influenza is a factor in the aetiology of an individual case of pneumonia is essentially retrospective. It consists in comparing the titre of antibodies against the influenza viruses in sera taken during the acute phase of the illness and in convalescence, normally about 2 weeks after the first sample Either the Hirst test (for antibodies inhibiting the agglutination of chick erythrocytes by the influenza virus) or the complement fixation test is generally used A rise of from two-fold to four-fold in titre is usually accepted as diagnostic

Treatment

The usual supportive treatment of pneumonias should be instituted Sulphonamides and antibiotics should be used to combat the secondary bacterial invasion, and controlled, according to the principles set out below, by the results of bacteriological examination of the sputum No statistics are yet available, however, to show how efficacious these measures are in the pneumonias associated with influenza.

In the fulminating influenzal pneumonias, the clinical picture is so distinctiv that a reasonable guess at the diagnosis can often be made even in apparent sporadic cases In such a case, since the outlook is generally so gloomy, enormo doses of antibiotics are justifiable, on the supposition that they may help by action at least upon the bacterial invader, which is often *Staphylococcus aure* Recovery has been recorded (Walshe, 1950) in such a case after the administrat of chloramphenicol (0 5 gramme four-hourly) and penicillin (1,000,000 u three-hourly)

PNEUMONIAS ASSOCIATED WITH MEASLES

In measles, as in influenza, the pneumonic complications are partly due associated bacterial infection

Pneumonia is the most serious complication of measles, and is especially in infants It most frequently takes the form of a basal broncho-pneu The mortality of measles pneumonia below the age of 2 years may be as 50 per cent Epidemics of measles in previously uninfected adult pop may also show a high incidence of complicating pneumonia, with a serious lower, mortality , such epidemics were observed in United States Arm in 1918 (Cole and MacCallum, 1918)

Symptoms and signs

The onset of symptoms of pneumonia complicating measles may n tinguishable from the catarrhal symptoms of severe measles On hand, there may be a fresh rise of temperature, with increased severity dyspnoea and sometimes pleural pain, after defervescence from th fever. Complications of the acute stage, such as empyema, depen

establishing the diagnosis If recovery of the virus is not possible, comparison of the titres of complement-fixing antibodies in acute-phase and in convalescent-phase sera will serve to establish the diagnosis. The rise is generally first evident between the eighth and the twelfth day of the illness It is important to establish a rise in titre, since the antibody is common to the whole lymphogranuloma-psittacosis-pneumonitis group, and a single observation of a high titre may therefore be attributable to a preceding infection by any of these viruses "Cold agglutinins" do not normally appear in the blood of patients convalescent from pneumonias of the psittacosis-ornithosis group, although exceptions to this rule have been recorded

Treatment

Large doses of penicillin (1,000,000 units or more daily) have been reported to be therapeutically effective, but aureomycin and, probably, chloramphenicol are more effective, and should be used

OTHER VIRUS DISEASES

There are other diseases known or presumed to be of virus origin in which pneumonia due to the causative virus may occur

Smallpox—In severe smallpox, specific lesions in the bronchi, accompanied by pneumonia with Guarnieri bodies in the lungs, have been recorded Howat and Arnott (1944) have recorded an outbreak of pneumonia, presumed to be of virus origin, in 7 cases between 11 and 15 days after contact with smallpox patients This remains an isolated observation and its precise significance is not clear

Chicken-pox—Several cases of severe chicken-pox in adults, with a pneumonia presumably due to the causative virus, have been recorded (Waring, Neuberger and Geever, 1942 , Claudy, 1947).

Lymphocytic chorio-meningitis—Two fatal cases of a severe disease with pneumonia, caused by the virus of lymphocytic chorio-meningitis, have been described by Smadel and his colleagues (1942)

Glandular fever—In severe cases of glandular fever (infectious mononucleosis) radiological evidence of pneumonia may be detected (Wechsler, Rosenblum and Silk, 1946) Occasionally, in patients who have been regarded as suffering from a pneumonia presumed to be of virus origin, a positive Paul-Bunnell test may be obtained, suggesting the possibility that the disease had been due to the virus of infectious mononucleosis.

PNEUMONIAS PRESUMABLY DUE TO UNIDENTIFIED PNEUMONOTROPIC VIRUSES

"Primary atypical pneumonia"

From about 1930 onwards, as radiography came to be used more and more as a

may occur Constitutional symptoms may be severe and include insomnia and delirium. Lung signs generally do not appear until after the fifth day ; they are indicative of a patchy lobular consolidation, showing a tendency to spread and become confluent The consolidation may be more evident radiographically than clinically In spite of extensive pulmonary consolidation, dyspnoea is less prominent than in bacterial pneumonias The leucocyte count is usually normal or low

Course—The recorded mortality in severe infections has been between 35 and 40 per cent, though it is probable that milder cases pass undiagnosed Death occurs most frequently during the second or third week of the illness.

Pathology—The consolidation is lobular in character, and the alveoli show considerable variation in their cellular content. The exudate consists chiefly of mononuclear cells, lymphocytes, plasma cells and macrophages ; polymorphonuclear leucocytes may be present in the terminal bronchioles. The bronchial epithelium is desquamated Inclusion bodies may be seen in the large phagocytic cells and in mononuclear cells in the alveolar walls. The mediastinal lymph-nodes are enlarged. The liver may show centrilobular necrosis. The spleen is usually slightly enlarged, and inclusion bodies may be seen in macrophages in the splenic sinuses.

Other vectors and related viruses

It has now been shown that viruses of the psittacosis group may be carried not only by parrots but also by other birds such as pigeons, finches, barn-yard fowls and fulmar petrels, and may be transmitted to man from these birds ; it has also been shown that certain small mammals may be infected with a virus of the same group and transmit the disease to man The name, ornithosis, has been applied to the disease transmitted to man from birds other than parrots. The relation between the viruses concerned is obviously very close, but whether they are variants of each other or distinct species remains uncertain There are well authenticated instances of transmission of the infection from human patients severely ill with pneumonia caused by this group of viruses to their attendants In general the clinical and pathological features of these pneumonias are similar to those of psittacosis, as described above A rather higher proportion of mild infections has been reported than in classical psittacosis, but this may be due to their having been discovered by specific investigation of groups of cases of pneumonia of undetermined aetiology, whereas psittacosis was not usually suspected unless the patient was gravely ill

Diagnosis

Clinically these cases are usually recognized in one or other of two ways. Sporadic cases come to light as the result of routine serological investigation of pneumonias in which no causative bacterial agent can be identified. Localized outbreaks of severe disease, with a pneumonia which is not due to any of the known bacterial agents, may lead to the application of laboratory tests for the identification of the causative agent

Demonstration of the virus, by inoculation of sputum, pleural fluid or blood intraperitoneally into mice during the acute stage, is the most positive way of

Course.—The severity of the illness varies greatly, even in localized outbreaks in closed communities, in which there is a reasonable presumption that the aetiological agent is the same in all cases In such outbreaks some cases may show no more than an upper-respiratory infection, others show evidence of involvement of the bronchi without pneumonia, others present as a rather more severe illness with radiological evidence of pulmonary consolidation but relatively brief fever, while a small number of patients have severe and prolonged illness with extensive pulmonary consolidation In general, in such outbreaks the milder cases predominate The mortality is extremely low, but a few fatal cases have been reported

Signs—The physical signs vary with the severity of the disease There may be evidence of inflammatory changes in the nose, pharynx, fauces and larynx In the lungs, some cases never show abnormal physical signs at any stage, others show no more than scattered rhonchi, others show localized areas of impaired percussion note, weakness of breath sounds and râles, while in others signs of frank consolidation may develop The physical signs may be variable from day to day, they may show very poor correlation with the extent of radiological changes In a small minority of cases the spleen is palpable, generally at the beginning of the illness

Radiographic changes—In general, radiographic changes become evident only several days after the beginning of the illness, usually from the second to the fifth day Two main types of change are observed In one group (Figs 28–31) the shadows are localized, usually not involving a whole lobe and sometimes involving parts of two or more lobes, they then present as homogeneous shadows with ill-defined edges, not usually corresponding to an anatomical lobe or segments, although occasionally a lobar or segmental distribution is observed. A rarer type of distribution, often associated with a more severe and prolonged illness, consists in small foci of consolidation scattered over more or less extensive areas of the lung fields, this is the so-called "disseminated focal" form Occasionally changes of both types are observed in the radiographs

Complications—Complications are usually rare Local complications, such as empyema, are very rare; when they occur they are due to secondary bacterial infection The most important complication, although it is extremely rare, is involvement of the central nervous system, presumably by the same virus as is responsible for the pneumonia, various forms of encephalitis and meningomyelitis have been described clinically and seen at necropsy An acute haemolytic anaemia is a possible though extremely rare complication, it is presumably a manifestation of an extreme degree of "cold agglutination" (*see below*), in which the cold agglutinin amounts to a haemolysin and gives rise to intravascular haemolysis in the cold extremities

Pathology

The number of necropsies recorded on cases of pneumonia which were shown to be neither psittacotic nor rickettsial in origin, and in which there is good evidence that they were due to unidentified pneumonotropic viruses, is limited Although the changes reported vary somewhat, certain general features can be made out There is usually a desquamating bronchitis in the larger bronchi, often with

routine part of the investigation of chest disease, it became clear that a large number of either apparently mild or moderately severe respiratory infections might lead to the development of a pneumonia, unaccompanied by the acute symptoms customarily associated with bacterial pneumonias From about 1940 onwards, there has been a tendency to use the term, " primary atypical pneumonia, aetiology undetermined ", to describe these cases, and it has been assumed frequently that the cases so described have been due to infection with pneumonotropic viruses, even though attempts to isolate such viruses have generally been unsuccessful

The illnesses which have been so described have been of very varied severity. Undoubtedly, especially among the earlier descriptions, there have been included some outbreaks due to viruses of the psittacosis group and to rickettsiae ; but, excluding these two specific types, the residue of the group still includes cases of very varied clinical pictures In general, the illnesses have started with evidence of upper-respiratory infection and fever, the relative prominence of the respiratory and the constitutional symptoms varying widely The common factor which unites the cases into a group is the evidence of pulmonary consolidations of very varied distribution and type, and often detectable only by radiography. These consolidations cannot be shown to be due to any of the bacteria known to cause pneumonia, their course is unaffected by treatment with sulphonamides or penicillin, and they are rarely of lobar distribution The prognosis is good although the duration of the illness is rather variable

It is probable that two fairly distinct groups of conditions have been described under this name The first which in Great Britain is probably the larger, is composed of cases which are examples of localized aspiration pneumonias, complicating a variety of acute or chronic respiratory-tract infections ; this group is discussed on page 122 The second is composed of cases in which there is good evidence to suggest that they are due to pneumonotropic viruses, although these usually remain unidentified It is with this second group that the following description deals The differential diagnosis of the two groups may be difficult , the points on which, in the present state of knowledge, judgment may be based are discussed below

Pneumonias of presumed but unidentified virus origin

Clinical picture

Symptoms —The earliest symptom may be an upper-respiratory infection, characterized by sore throat and coryza , on the other hand, in some cases febrile symptoms predominate at the onset Within a few days cough develops, generally not productive at first, but later productive of scanty mucoid or mucopurulent sputum Blood-stained or rusty sputum is rare The cough is often paroxysmal and distressing There may be pain and discomfort in the chest, but these are rarely of a pleuritic type The character and height of the fever are very variable The pulse is generally raised in proportion to the temperature, but the respiration rate is only slightly raised, if at all, in contrast with what is observed in bacterial pneumonias The duration of the febrile period varies from a few days to 4 or 5 weeks

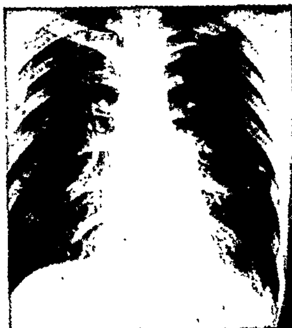


FIG 30.—Same case as in Fig 28, appearance on twenty-sixth day

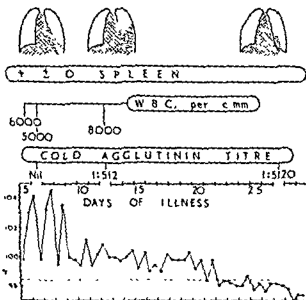


FIG 31.—Graphic record of the course of the case of pneumonia due to an unidentified virus illustrated radiographically in Figs 28, 29 and 30



Fig. 28—Pneumonia due to unidentified virus, sixth day of illness.

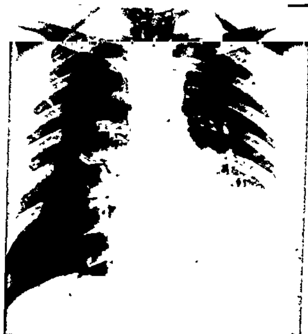


Fig 29—Same case as in Fig 28 on thirteenth day of illness.

the most firmly established. However, this virus is difficult to work with, and the illness associated with it appears to be mild and to have a relatively low incidence of pneumonic changes It is highly probable that other agents as yet unidentified are responsible for the majority of cases in this group Experiments in human transmission have provided suggestive evidence that a virus causing pneumonia can be transmitted from man to man, but the results of the published experiments should be interpreted with considerable caution

" Inclusion-body " pneumonias in infants

Adams and his associates have reported on several epidemics of pneumonia in infants, which they believed to be of virus origin (Adams, 1941 ; Adams and his co-workers, 1942) This view was supported by the epidemiology and by the presence of cytoplasmic inclusion bodies in the epithelial cells of the respiratory tract Attempts to isolate the presumed virus have, however, been unsuccessful

Diagnosis

The diagnosis of a pneumonia of this type can usually be reached only by exclusion The clinical picture may be suggestive The presence of radiological changes indicative of fairly extensive pneumonia in a patient with relatively mild respiratory symptoms is suggestive, especially if there is a prolonged course distinguishing the condition from a localized aspiration pneumonia Other forms of pneumonia are excluded by the failure to find causative agents , appropriate tests for psittacotic, rickettsial and influenzal infections should be done before concluding that a pneumonia belongs to the group of those due to unidentified viruses The presence of a high and rising titre of cold agglutinins, or of agglutinins against streptococcus MG, is a point of value in confirming the diagnosis, but its absence does not negate the diagnosis Failure to respond to sulphonamides and penicillin is also a suggestive point, but, of course, is not diagnostic, because several of the rarer forms of bacterial pneumonia, as well as rickettsial and psittacotic pneumonias, also fail to respond adequately to these agents. The differential diagnosis of pneumonias presumed due to *pneumonotropic* viruses from localized aspiration pneumonias is discussed below

Treatment

These pneumonias usually respond favourably to aureomycin, chloramphenicol and terramycin

RICKETTSIAL PNEUMONIA

In the various forms of typhus fever, lung changes due to the causative rickettsia may be incidental findings in severe cases, but they probably contribute little to the total clinical picture of the disease On the other hand, the lung changes associated with Q fever, a rickettsial disease of much milder character, are an important feature of the illness, which, in fact, is frequently diagnosed as an " atypical pneumonia ".

Q fever was first described in 1937 in Queensland (Australia) and resembles a mild form of typhus with extremely low mortality , it is transmitted, like typhus, by an arthropod vector from small mammals A similar illness, caused by a rickettsia having similar characteristics, was described in Montana (U S A)

purulent exudate, while in the smaller bronchi the exudate contains mononuclear cells The interstitial tissues are usually infiltrated with mononuclear cells, and in some instances there are changes in the smaller bronchial arteries—either necrosis and cellular infiltration of their walls or thrombosis. In zones of consolidation, the exudate is mainly mononuclear Bacteria, if present, are found only in the larger bronchi, where they seem to be responsible for the polymorphonuclear exudate

Cold agglutinins

In some cases of this group, the blood shows the phenomenon of " cold agglutination " This consists in auto-agglutination of the red cells by the plasma as soon as the blood reaches room temperature, and is reversible on warming the blood again to body temperature It has been recognized for many years as a rare anomaly, occurring in certain blood dyscrasias, in some forms of *peripheral vascular disease, and occasionally in hepatic and splenic disease;* [illegible] In the most extreme examples the red

of the highest titre at which a dilution of the patient's serum will agglutinate normal group-O red cells on exposure to cold If cold agglutinins appear in a case of presumed virus pneumonia, the titre generally starts to rise during the second week of the illness, and possibly only after clinical recovery; it reaches its maximum during the third or fourth week

The phenomenon, however, is inconstant Some outbreaks of presumed virus pneumonia show a high incidence of " cold agglutination ", and in these it has sometimes been observed that patients with mild illnesses, confined to the upper respiratory tract and never involving pneumonia, develop a high titre of cold agglutinins In other outbreaks, which otherwise seem little different, " cold agglutination " appears not at all or only rarely Thus, although the development of a high and rising titre of cold agglutinins in a case of pneumonia lends support to the hypothesis of a viral origin, the test is not specific, and the absence of cold agglutinins does not refute this hypothesis

The appearance of an agglutinin for some strains of indifferent streptococci, *notably that designated MG, has also been observed in some cases of pneumonias* of this group, in general the appearance of this phenomenon seems to be related to the appearance of cold agglutinins Although the streptococcus MG is a strain originally isolated from cases of " primary atypical pneumonia ", there *is nothing to suggest that this organism has any causative relation* to the disease, and the significance of the appearance of agglutinins against it remains unknown

Aetiology

Many attempts have been made to isolate specific viruses from patients suffering from pneumonias of this group This work has been much hampered by the presence of many latent pneumonotropic viruses in the experimental animals (mice, hamsters, cotton-rats and rabbits) commonly used Of all the agents reported, that isolated by Eaton and others in 1942 and subsequently fairly completely investigated (Eaton, Meiklejohn and van Herick, 1944), seems to be

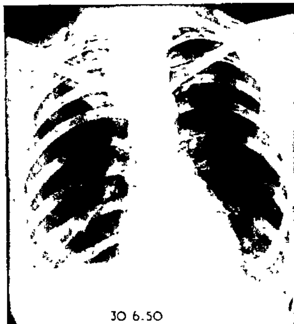


FIG 32.—Pneumonia due to *R burneti* (Q fever), sixth day of illness The apical localization is unusual, but the consolidation may be at any site

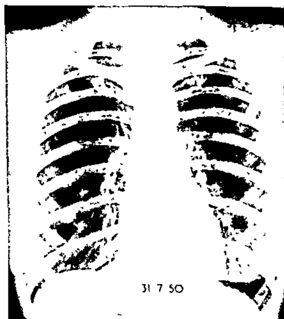


FIG 33.—Same case as in Fig 32, one month later, showing complete resolution

in 1938, and the rickettsiae of the Australian and American cases were shown to be identical; this organism has received the name, *Rickettsia burneti.*

Epidemiology

The next step in the recognition that *R. burneti* might be a cause of obscure pneumonic illnesses arose when a number of outbreaks of febrile disease associated with pneumonic consolidations, occurred in workers in laboratories in which the rickettsia was being investigated, and these illnesses were shown to be due to the organism. In 1946 an outbreak of a febrile illness with pneumonia was observed in American troops returning from Italy, and was shown to be due to Q fever. At the same time, serological investigations showed that several outbreaks which had occurred among troops in Italy and Greece, and had been generally diagnosed as "atypical pneumonia", were due to the same cause. Moreover, considerable proportions of small groups of the civilian population in the areas in which these epidemics had occurred were shown to have significant titres of complement-fixing antibodies against *R burneti.* Other retrospective serological investigations have shown that outbreaks of so-called "atypical pneumonia" in New Zealand troops in Italy had probably been due to Q fever. Subsequently it has been shown serologically that Q fever is probably locally endemic in widely scattered parts of the world. Several endemic foci have been found in Great Britain, and small outbreaks as well as sporadic cases have been reported.

The exact source of infection in most of these outbreaks is unknown There is suggestive evidence of close contact with cattle in most cases; rickettsial antibodies have been demonstrated in the blood of cattle, and *R burneti* has been isolated from milk It is possible that, although direct transmission by an [illegible]

[illegible]

infection into the human subject, in most instances, through the respiratory tract, in infected dust or in other particulate matter. Infection has been acquired in some instances by handling infected eggs in laboratories or by simple attendance at post-mortem examinations on fatal human cases

Clinical picture and diagnosis

Clinical aspects —The severity of the symptoms in cases of pneumonia due to *R. burneti* is variable. In most cases the onset is abrupt with malaise and chilly sensations; the fever is variable in duration *from 4 days to 2 or 3 weeks*; *severe* [illegible] Apart from anorexia, gastro-intestinal [illegible], commonly develop after several [illegible] In some outbreaks *pleuritic pain* has been described. The physical signs in the lungs are usually much less remarkable than the radiographic appearances. About the fourth day, localized râles, impairment of percussion note or weak breath sounds may be found in any part of the lung fields Radiography shows diffuse ill-defined shadows in one or both lung fields (Figs 32 and 33). In some cases the illness consists only of a brief fever without evidence of lung involvement. In a few cases enlargement of the spleen has been reported, but this appears to be rare.

not rise The physical signs consist in (1) tachypnoea and cyanosis, (2) impairment of percussion-note at the bases of the lungs, (3) weak breath sounds, sometimes with patches of bronchial breath sounds, and (4) medium râles; there may be generalized rhonchi

Treatment —Prophylaxis is important, and consists in frequent changes of posture, encouragement and help in coughing, and, in suitable cases, gentle inspiratory breathing exercises or the administration of carbon dioxide (7 per cent in oxygen), until an observable hyperpnoea develops, every 1–2 hours In treatment, the same measures, where possible, are helpful Oxygen is required for the treatment of anoxia Penicillin should be given to combat the bacterial infection; but the mechanical measures are generally more important.

Inhalational pneumonias

Inhalation pneumonias are due to the aspiration into the lungs of infected or irritant substances from outside the respiratory tract Infected water and particulate matter may be aspirated after immersion in water and cause an aspiration pneumonia after resuscitation from drowning Gastric contents may be aspirated during anaesthesia, food may be aspirated by patients with disturbances of pharyngeal function, such as paralysis or loss of sensation of the larynx, growths involving the larynx or pharynx, or oesophageal obstruction from any cause (" deglutition pneumonia ")

The pneumonia so caused is generally diffusely lobular in distribution and affects especially the bases and the posterior parts of the lungs Especially in those forms associated with aspiration of gastric contents or food, or with septic lesions of the pharynx, the lesions may suppurate if the patient lives long enough Prognosis depends principally upon the antecedent condition, and treatment is on the lines suggested for hypostatic pneumonias

The inhalation pneumonias associated with chronic dysphagia are of special importance, the dysphagia may be due to such causes as achalasia of the cardia, oesophageal pouches (Fig 34) or carcinoma of the oesophagus (Figs 35 and 36) Aspiration of material spilt over from the oesophagus into the lower respiratory tract gives rise to acute inflammatory incidents, ranging in severity from transient pneumonic reactions to foetid lung abscesses, and repeated incidents of this sort may eventually give rise to chronic fibrotic changes especially at the bases and posterior parts of the lungs, and to chronic broncho-pulmonary suppuration with bronchiectasis (Belcher, 1949) If there is a clear history of dysphagia, the diagnosis is easy, but in some cases, direct inquiry will be required to elicit the history of this symptom, and in all cases radiography after barium swallow should reveal the underlying oesophageal abnormality

Localized aspiration pneumonias

Aetiology

Localized aspiration pneumonias occur in acute or chronic, infective or non-infective, catarrhal conditions of the respiratory tract—that is to say, whenever there is an excess of mucoid or muco-purulent secretions in the respiratory tract, and the ciliary and other defence mechanisms are depressed These pneumonias are most frequently seen in association with acute upper-respiratory infections,

Diagnosis.—The diagnosis of rickettsial pneumonia depends upon laboratory findings The most generally useful are rickettsial agglutination or complement-fixation tests, which show a rise in titre during the second week and reach their peak several weeks later. In order to establish the diagnosis as firmly as possible, a comparison of the titres of sera taken during the acute stage (that is to say, the first week) and during the third week or later is desirable Occasionally it may be possible to isolate the rickettsia by animal inoculation with blood or serum during the earlier stages of the illness Cold agglutinins do not appear in the blood—a point which may be suggestive in distinguishing Q-fever pneumonias from some of the pneumonias presumed to be due to unidentified pneumonotropic viruses (*see* page 113)

Course and treatment

The mortality is very low. The infection does not respond to penicillin or sulphonamides, but the fever can generally be cut short by administration of aureomycin, terramycin or chloramphenicol

ASPIRATION PNEUMONIAS

Aspiration pneumonias are due to failure of the normal defences of the respiratory tract, allowing organisms not specifically pathogenic to gain access to pulmonary acini These pneumonias are a consequence of the obstruction of lobular, segmental or lobar bronchi by infected secretions or irritant or infected unorganized material from outside the respiratory tract, and are thus closely related to atelectasis. They can be divided into three groups · (1) diffuse, (2) localized and (3) suppurative. The last constitutes an important group of lung abscesses, and are not considered further in this section

Diffuse aspiration pneumonias

Diffuse aspiration pneumonias can be divided into two principal types, (1) hypostatic and (2) inhalational

Hypostatic pneumonias

These arise in patients enfeebled by severe illness, especially after long confinement to bed, and in the aged Feeble respiratory movements of the diaphragm and chest wall, together with depression of the cough reflex, enable secretions to [illegible]

[illegible] and may include pneumococci, usually of the higher types Thus a patchy consolidation or broncho-pneumonia develops , if the condition is not relieved it may become confluent. An intercurrent upper-respiratory infection is sometimes a contributory factor in the initiation of the pneumonia. The gravity of the clinical picture depends principally upon the gravity of the primary illness Hypostatic pneumonia is frequently a terminal event.

Clinical features.—With the onset of a hypostatic pneumonia, the chief symptoms are (1) a feeble, largely ineffective cough, (2) dyspnoea and (3) cyanosis. The temperature, which may have been elevated by the primary disease, may or may



FIG 36 —Barium swallow in same patient as in Fig 34, showing carcinoma of oesophagus with perforation of trachea

with chronic bronchitis, with chronic nasal sinusitis and with asthma They may be regarded as mildly infected atelectases of one or more broncho-pulmonary segments

Clinical picture

The symptoms may not be very distinctive, suggesting only an acute respiratory catarrhal infection or an exacerbation of a more chronic one A common history is that the patient has had a recent " cold in the nose " or a similar acute upper-respiratory infection, this has led to the development of a cough with expectoration, which is slow to clear up, and there may have been some slight pleuritic pain or even slight blood-staining of the sputum The patient feels generally unwell and usually loses some weight, but may or may not feel ill enough to take to his bed A similar sequence of events may occur in a patient with a chronic nasal catarrh or nasal sinusitis A localized aspiration pneumonia may occur in a chronic bronchitic subject, the history is then that there has been an exacerbation of the cough and expectoration, followed by malaise, loss of weight and pain in the chest, and occasionally by slight haemoptysis

Physical signs are rarely distinctive The patient is not acutely ill, but is usually lacking in energy, and is slightly dyspnoeic on exertion but not at rest; the temperature may or may not be slightly elevated In the chest, slight impairment of percussion note, weak breath sounds and a few râles constitute the maximal abnormality to be expected, and sometimes no localizing sign is to be found on the most critical examination In the bronchitic group, the physical signs of the underlying bronchitis will be evident

Radiography is usually necessary to establish the diagnosis, and until radiography

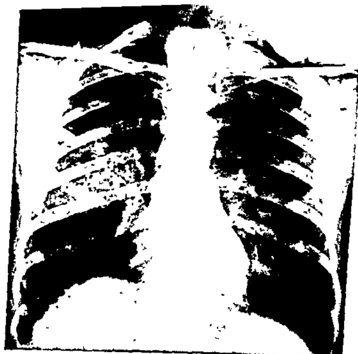


FIG 34 — Aspiration pneumonia in association with oesophageal pouch



FIG 35 —Aspiration pneumonia in a man aged 55 who had no dyspeptic symptoms



FIG 38 —Lateral view of case shown in Fig 37, showing localization in the apical segment of the lower lobe, into which secretions trickling down the trachea and main bronchi gravitate in a subject lying on his back

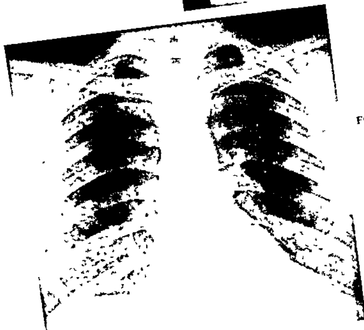


FIG 39 — Same case as in Fig 37 showing resolution The patient remained ambulant throughout, compare with the course of the virus pneumonia illustrated in Figs 28-31



FIG 37 —Localized aspiration pneumonia This occurred in a man who had a respiratory infection of "common cold" type, after a barbiturate had caused a night's deep sleep in which he had lain on his back

as routinely used in the investigation of such conditions, their true nature :mained unsuspected Radiography shows sub-lobar areas of consolidation, hich can be shown by examination in two planes to be segmental in distribution ⁻igs 37–39) The consolidation is not necessarily uniform throughout the ffected segment or segments, it may be diffusely lobular in distribution within the :gment from the beginning, or, if radiography is not carried out until late in the ɔurse of the disease, the opacity may be mottled because of irregular resolution ıd re-expansion within the affected segment

athogenesis

The most reasonable hypothesis to account for these pneumonias is that ıey are due to bronchial obstruction by mucus, followed by the develop- ıent of an atelectasis of the part of the lung supplied by it, infected by organisms hich chance to be present in the mucus That mucus can, in fact, trickle down ıto the bronchi during sleep is suggested by the observation that iodized oil, ropped into the nose of a sleeping person, can be shown radiographically ı be present in the lungs on the following morning In many cases, the ɔurse of events leading up to development of a localized aspiration pneumonia initiated by an upper-respiratory-tract infection presumably of virus origin, ut there is *in these cases no evidence to suggest that the pneumonia itself is due*

benign course of the aspiration pneumonia will generally lead to a correct diagnosis without undue delay.

Treatment

Treatment is on general lines Most patients are not acutely ill and are usually ambulant, and for them sulphonamides and antibiotics are usually not required, since the infection is not specific Symptomatic treatment for troublesome symptoms, such as cough, may be required The more ill patients may require to be kept in bed for a few days, and in such cases a short course of a suitable sulphonamide or of penicillin may be advisable In general, breathing exercises to encourage re-expansion of the infected atelectatic segment will do more than any other measure to hasten resolution It is most important to verify complete resolution radiologically, in view of the many differential diagnostic problems which may arise.

TREATMENT OF PNEUMONIAS

In dealing with the practical problem of the treatment of a case of pneumonia, ... that the infecting agent is known with certainty at the beginning; ... take steps which may lead to the sub- ... by methods ... necessary ... about the ... applicable ... s and with ... h sulpho... ... of pneumonia,

General measures applicable to a... ... en adequate

The patient with acute pneumonia must be kept in bed ... nursing care Methods of specific treatment are now so effective in most forms of pneumonia that the majority of patients can be nursed successfully at home Nevertheless, if there is any doubt about the feasibility of this, or if there is any reason to fear that the course will be complicated, a decision should be made as early as possible whether the patient is to be nursed at home or in hospital The disturbance associated with moving a patient late, after attempts at specific treatment have failed or complications have arisen, is much greater than that associated with transfer to hospital as soon as the diagnosis is made

Nursing.—In any case, the patient should occupy a well-ventilated room, ... at an equable temperature at about 65° F Most ... th pillows, but some ... hould decide the ... anges of position ... ects In addition ... a record of fluid intake ... lphonamide ... equently ... y disease ... on the patient

K

to a virus, similar localized aspiration pneumonias occur in the course of chronic catarrhal affections not associated with any specific infection, such as chronic bronchitis, asthma and nasal sinusitis

Relation to lung abscess—One of the commonest types of lung abscess is initiated by bronchial obstruction by infected secretions, and may in fact be regarded as a ...

... is process has been ... he refers to it as ... rial flora of the obstructing material and in the patient's ...

the type of lesion wh...

the benign localized ...

suppurative lesions ...

obstruction by infected endogenous secretions clarifies many problems in the pathology of the lungs

Prognosis and diagnosis

The course is usually benign, the consolidation clearing up without incident within a few days or weeks Many patients with such lesions are treated by general practitioners and given a diagnosis of "feverish colds", "bronchitis", "pleurisy" or "abortive pneumonia", because, unless radiographs are taken, the lung lesion is unlikely to be detected. Often the condition first comes to light when a patient whose "cold" seems to be slow in clearing up, but who has been ambulant throughout the illness (except perhaps for a day or two), is referred by his doctor to a consultant

Differential diagnosis—This is important. Localized aspiration pneumonias must be distinguished (1) from specific pneumonias, bacterial and virus, (2) from pulmonary tuberculosis, (3) from suppurative pneumonias or lung abscesses, and (4) from new growths of the bronchus

The history and the absence of acute illness serve to distinguish the condition from acute specific pneumonias in most instances The failure to find appropriate bacteria in the sputum is helpful in the diagnosis from bacterial pneumonias Influenzal and psittacotic pneumonias produce a more severe illness, often in epidemic form A diagnosis of pneumonia due to an unidentified pneumonotropic virus is more likely when constitutional symptoms are prominent, and if some of the lung lesions can be shown to be non-segmental, it may be supported by the finding of a high titre of cold agglutinins in convalescence, and by the presence of a local epidemic of similar cases. The diagnosis from pulmonary tuberculosis ...

... the

stage of a suppurative pneumonia ... the

possibly more severe illness, as ... g to

lungs start by exactly the same m... infected atelectasis, and in many instances only observation and serial radiography will determine whether or not the lesion will suppurate. New growths of the bronchus are simulated only by the more extensive localized aspiration pneumonias; in such a case bronchoscopy may be of diagnostic value, and the

in a dose of 2–3 drachms (7.5–11.0 millilitres) in a mixture flavoured with syrup of orange or in ½ fluid ounce (30 millilitres) of whisky or brandy; alternatively, paraldehyde can be given *per rectum*, 4–6 drachms (15–22.5 millilitres) in 6 ounces (180 millilitres) of water.

Control of delirium.—Delirium may require treatment. Relief of pyrexia by tepid sponging and of anoxia by oxygen administration may be effective. Phenobarbitone soluble (Sodium Luminal), 1–2 grains (60–120 milligrams) subcutaneously, or paraldehyde *per rectum*, as suggested above, may be helpful. To patients known to be alcohol addicts, whisky or brandy, ½ fluid ounce (30 millilitres) four-hourly should be given if there is delirium; otherwise alcohol is of no value in the treatment of pneumonia.

Control of cough.—Distressing and ineffective cough should be controlled with a suitable linctus containing codeine, or, in more troublesome cases, Physeptone or diamorphine (diacetylmorphine, heroin). A productive cough is to be encouraged by supporting the patient during bouts of coughing, by simple postural methods if the general condition permits, and by the relief of pleural pain.

Treatment of meteorism.—Abdominal distension may become troublesome. In such cases treatment should be started with administration of a simple soap enema, and the passage of a flatus tube. If these measures are not sufficient, turpentine or bile enemas and the administration of pituitary extract (0.5 millilitre), or of Prostigmin (1 milligram), subcutaneously may be effective. The administration of oxygen, in a concentration as near 100 per cent as possible, from a B.L.B. or similar mask, may lead to diminution of the distension by causing absorption of the gases into the blood stream.

Oxygen administration.—The anoxaemia of pneumonia is due to factors of several sorts, some of which can be relieved by administration of oxygen. It is probably responsible for many of the so-called toxic symptoms. To any cyanosed patient, therefore, oxygen should be administered by an effective method. This applies particularly to those forms of pneumonia which are complicated by much bronchitis. An efficient mask of the B.L.B. type, or a tent, should be used.

Cardiovascular system.—Pneumonias affect the heart mainly indirectly, through peripheral vascular effects and through anoxia, although there may be some direct toxic effect on the myocardium. There is no justification for the routine use of drugs alleged to have an effect on the heart. In particular, digitalis should be given only if an abnormal rhythm develops, and should then be used in the manner appropriate to the treatment of this condition. The form of circulatory collapse most commonly seen in patients gravely ill with pneumonia presents a picture of falling blood pressure with a rising regular pulse rate. Digitalis and similar drugs have no effect in cases of this sort. Analeptics, such as camphor, nikethamide, and Cardiazol, are widely used to combat this condition; but since its essential cause is a peripheral vasomotor failure, and since any stimulating effect that may be produced by these agents is of central origin, their value is doubtful. Adequate oxygen therapy and the administration of glucose are the most rational procedures.

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Diet—In the acute stages of pneumonias, the patient usually has comple loss of appetite and, as the duration of the disease is short, there is little point i attempting to force unwanted food upon him, provided that an adequate intak of fluid and carbohydrate is maintained For an adult, a total fluid intake o about 2,500 millilitres (4 pints) daily is suitable. Part of this may be given i the form of drinks sweetened with as much glucose or cane sugar as the patient' taste will permit, flavoured with lemon or orange or grape-fruit juice, and mad up with plain water or soda-water to taste. Milk, hot or cold, preferably wit extra sugar added, and flavoured in any acceptable way, may be given, but no more than 2 pints daily If the patient does not like sweet drinks, lactose may b used in his drinks instead of glucose or cane sugar , lactose may also be usefu in cases with abdominal distension, because it gives rise to less intestinal fermen tation Eggs, cereals, custards, thin buttered bread or toast, fish, minced lea meat or chicken, mashed potato and vegetable *purées* can be added when th patient's condition permits If it becomes clear that, on account of a complica tion such as empyema, a prolonged febrile illness is likely, the diet should be more strictly controlled, with due attention to calorie and vitamin content

Relief of pain.—
in the form of a
such a way as to
severe, morphine or other opium derivatives or pethidine may be required (*see below*) Occasionally the pleural pain may be extremely severe, and if in such a case it is well localized the injection of 5–10 millilitres of 2 per cent procaine, just external to the parietal pleura in the painful area, may be helpful.

Relief of sleeplessness—If insomnia is not due to pleural pain, adjusting the patient's position, making him comfortable in bed, and giving a hot drink and a simple hypnotic may be sufficient to secure sleep. In this case, the well-tried combination grains (1·2 grammes) of each, or a –6 grains (0·18–0·36 gramme) may ss, pleural pain and irritating unproductive cough, however, often demands the use of morphine or one of its analogues to secure sleep. The only danger of these drugs arises from their depressing action on the respiratory centre and on the intestinal motility. Hence, for patients with cyanosis due to a complicating bronchitis, or with any tendency to abdominal distension, their use should be avoided For all other patients morphine, $\frac{1}{6}$–$\frac{1}{4}$ grain (10–15 milligrams), or pethidine, 25–50 milligrams hypodermically, can be used quite safely, if necessary, to secure sleep. If ineffective cough is the chief obstacle to sleep, codeine phosphate, $\frac{1}{2}$–1 grain, (30–60 milligrams) may be sufficient If it is considered necessary for the relief of pain and to secure sleep to give morphine to a cyanosed patient, oxygen should also be given by an efficient method If there is so much complicating bronchitis or severe abdominal distension that morphine and its analogues are contra-indicated, paraldehyde is generally the most useful hypnotic. It may be given by the mouth

in a dose of 2–3 drachms (7·5–11 0 millilitres) in a mixture flavoured with syrup of orange or in ½ fluid ounce (30 millilitres) of whisky or brandy, alternatively, paraldehyde can be given *per rectum*, 4–6 drachms (15–22·5 millilitres) in 6 ounces (180 millilitres) of water

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such a way as to avoid [illegible]
severe, morphine or other opium derivatives or pethidine may be required (*see below*) Occasionally the pleural pain may be extremely severe, and if in such a case it is well localized the injection of 5–10 millilitres of 2 per cent procaine, just external to the parietal pleura in the painful area, may be helpful.

Relief of sleeplessness.—If insomnia is not due to pleural pain, adjusting the patient's position, making him comfortable in bed, and giving a hot drink and a simple hypnotic may be sufficient to secure sleep In this case, the well-tried combination of chloral hydrate and potassium bromide, 20 grains (1 2 grammes) of each, or a simple barbiturate, such as Sodium Amytal, 3-6 grains (0 18–0 36 gramme) may be sufficient. The combination of restlessness, pleural pain and irritating unproductive cough, however, often demands the use of morphine or one of its analogues to secure sleep The only danger of these drugs arises from their [illegible] Hence,

[illegible]

dermically, can be used quite safely, if necessary, to secure sleep [illegible] neffective cough is the chief obstacle to sleep, codeine phosphate, ½–1 grain, (30–60 milligrams) may be sufficient If it is considered necessary for the relief of pain and [illegible]

in a dose of 2–3 drachms (7 5–11 0 millilitres) in a mixture flavoured with syrup of orange or in ½ fluid ounce (30 millilitres) of whisky or brandy; alternatively, paraldehyde can be given *per rectum*, 4–6 drachms (15–22 5 millilitres) in 6 ounces (180 millilitres) of water

Control of delirium—Delirium may require treatment. Relief of pyrexia by tepid sponging and of anoxia by oxygen administration may be effective Phenobarbitone soluble (Sodium Luminal), 1–2 grains (60–120 millilitres) subcutane- [illegible] To patients [illegible] 30 millilitres) [illegible] is of no value in the treatment of pneumonia

Control of cough.—Distressing and ineffective cough should be controlled with a suitable linctus containing codeine, or, in more troublesome cases, Physeptone or diamorphine (diacetylmorphine, heroin) A productive cough is to be encouraged by supporting the patient during bouts of coughing, by simple postural methods if the general condition permits, and by the relief of pleural pain

Treatment of meteorism—Abdominal distension may become troublesome In such cases treatment should be started with administration of a simple soap enema, and the passage of a flatus tube If these measures are not sufficient, turpentine or bile enemas and the administration of pituitary extract (0 5 millilitre), or of Prostigmin (1 milligram), subcutaneously may be effective The administration of oxygen, in a concentration as near 100 per cent as possible, from a B.L B or similar mask, may lead to diminution of the distension by causing absorption of the gases into the blood stream

Oxygen administration—The anoxaemia of pneumonia is due to factors of several sorts, some of which can be relieved by administration of oxygen. It is probably responsible for many of the so-called toxic symptoms To any cyanosed patient, therefore, oxygen should be administered by an effective method This applies particularly to those forms of pneumonia which are complicated by much bronchitis An efficient mask of the B L B type, or a tent, should be used

Cardiovascular system—Pneumonias affect the heart mainly indirectly, through peripheral vascular effects and through anoxia, although there may be some direct toxic effect on the myocardium There is no justification for the routine use of drugs alleged to have an effect on the heart In particular, digitalis should be given only if an abnormal rhythm develops, and should then be used in the manner appropriate to the treatment of this condition. The form of circulatory collapse most commonly seen in patients gravely ill with pneumonia presents a picture of falling blood pressure with a rising regular pulse rate Digitalis and similar drugs have no effect in cases of this sort. Analeptics, such as camphor, nikethamide, and Cardiazol, are widely used to combat this condition, but since its essential cause is a peripheral vasomotor failure, and since any stimulating effect that may be produced by these agents is of central origin, their value is doubtful Adequate oxygen therapy and the administration of glucose are the most rational procedures.

Specific treatment

Practical considerations

In the case of apparently primary pneumonias of lobar extent, the pneumococcus is so frequently the causative organism that, pending an aetiological diagnosis, it is reasonable to treat all cases of this sort in the first instance as if they were caused by the pneumococcus; but, whenever possible, material should be obtained for bacteriological examination before beginning treatment. Sputum, if a good specimen is available, is the best material and can generally be obtained by encouraging the patient to cough. If it is quite unobtainable, a throat or laryngeal swab may give useful information but is less reliable. Lung puncture is justifiable only for special purposes. In any gravely ill patient a blood culture should also be carried out before treatment is begun. If there is any reason to suspect a virus pneumonia, and appropriate laboratory facilities are available, a specimen of blood should be taken during the acute stage, and the serum preserved in the cold for possible future serological tests; titres of the various antibodies do not usually rise until convalescence, but the detection of a rising titre, by comparison of acute-stage and convalescent sera, provides more convincing evidence than does a single observation of a high titre during convalescence.

Choice of specific remedy

The choice of specific agents having a wide range of activity is becoming rather large, and decision will often be determined to some extent by questions of availability and convenience. The sulphonamides have the advantages of convenience of administration, low cost and ready availability. There are several sulphonamides effective against the pneumococcus, the haemolytic streptococcus and, to a less extent, *Staphylococcus aureus*. Their disadvantages include (1) their tendency to cause toxic effects, such as nausea and vomiting, (2) renal damage by precipitation of crystals of their acetyl derivatives in renal tubules; (3) sensitivity reactions, such as skin rashes, drug fever, and agranulocytosis and other blood disorders. They have no effect on viral or rickettsial pneumonias. Penicillin has the advantage of almost complete freedom from toxic effects, and of a wider range of activity against bacteria, including staphylococci; its disadvantage is the necessity for *administration by intramuscular injection*. It is ineffective against Friedlander's bacillus, against viruses (with the possible [illegible] Aureomycin, [illegible] against bacteria, [illegible] penicillin; they are also active against viruses of the psittacosis-ornithosis group and those associated with *unidentified viral pneumonia* and against rickettsiae; they are administered by the mouth, and they have few toxic effects. Their effectiveness *in the various types of pneumonia*, as compared with each other and with other agents, is not yet fully established, but it appears possible that among them may be found the drug of choice for the treatment of most pneumonias. At present, their high cost and scarcity in most parts of the world militate against their general use. The methods of administration of these various agents and any special indications for their use will next be considered.

than that of penicillin or sulphonamides, they have a special indication in pneumonias due to viruses and to rickettsiae The difficulty is that the diagnosis of these pneumonias usually can only be suspected in the acute stage, awaiting retrospective proof by serological investigation during convalescence Hence, aureomycin, terramycin or chloramphenicol should be given to any patient with an acute pneumonia in whose case there is reasonable suspicion, on the clinical grounds discussed in the description of the viral and rickettsial pneumonias, to suppose that the illness is due to one of them Quite often, these clinical grounds may include the failure of sulphonamides and penicillin to affect the course of the disease after 48 hours or so of adequate dosage, especially if other drugs are not readily available

An investigation of the relative value of aureomycin, chloramphenicol and standard treatment with penicillin and sulphonamides in the treatment of patients with a *primary clinical diagnosis of pneumonia* has been carried out under the aegis of the Medical Research Council (1951) The newer antibiotics presented no advantage in statistical results over penicillin, their side-effects were more frequent and more troublesome ; and in the group of very ill patients in whom the mortality is highest, the fact that penicillin is injected is a great advantage. Hence, it seems reasonable to attempt to reserve the newer antibiotics, as suggested above, for those cases in which there is some evidence that the pneumonia is due to an agent insusceptible to penicillin

Indications for changing treatment

If there is a poor response to the chosen initial treatment, with no improvement

poorly sensitive or not sensitive to the agent used, may be present for example, *Staph aureus* in a patient under treatment with a sulphonamide, or Friedlander's bacillus in a patient treated with penicillin Alternatively, there may be no bacterial pathogen in a patient under treatment with a sulphonamide or penicillin ; in this case, the clinical aspects should be reviewed with special reference to the *possibility of a virus infection* Whenever indicated by such considerations, an appropriate change in specific therapy should be made If there is no clear indication of the probable aetiology on these grounds, the *diagnosis should be reviewed*, bearing in mind the possibilities that the pneumonia may be an acute tuberculous one (which may not be shown by the direct examination of a sputum-smear, which is the only source of bacteriological information at this stage), that it may be secondary to bronchial obstruction by new growth or foreign body ; that it may be the earliest stage of a suppurative pneumonia or lung abscess, finally, that acute tuberculous pleural effusions and pulmonary infarctions are sometimes misdiagnosed and treated initially as pneumonias If all these possibilities can be excluded, local complications, especially the early (syn- ...) development of empyema, should be considered ; if there is any

are secondary to disease elsewhere: for example, to sub-phrenic suppuration, to infective endocarditis or to general pyaemia

The treatment of aspiration pneumonias

In these pneumonias, treatment will be dependent upon which of the many types of this group is under consideration In all pneumonias of this group there is a considerable mechanical factor, early attention to which may cause rapid alleviation of the condition before there has been any severe invasion by bacteria, although infection by specifically invasive organisms may occur at any stage

Localized aspiration pneumonia

In the mildest types, the localized aspiration pneumonias, the patient may be ambulant and, in such cases, breathing exercises for a few days may be all that is required If the patient is rather more ill with some fever, a few days in bed, with simple sulphonamide or penicillin treatment and breathing exercises, will produce rapid recovery

Diffuse aspiration pneumonia

The treatment of the more severe cases of diffuse aspiration pneumonia may be exemplified by the treatment of post-operative or hypostatic broncho-pneumonia Although in such cases it is wise to start, as with apparently primary pneumonias, by obtaining material for bacteriological examination and instituting standard sulphonamide or penicillin therapy, the mechanical factors should receive immediate careful attention The patient must not be allowed to remain constantly in the unfavourable posture which he will naturally tend to adopt He will most often be found lying in the position which prevents him from coughing: that is to say, the position in which the affected part of the lung is least favourably placed for the expulsion of secretions He should be made to change his position into a more favourable (and probably less comfortable) one, and encouraged to cough Voluntary deep breathing is helpful, administration of 7 per cent carbon dioxide in oxygen may have a comparable effect on uncooperative patients No tight bandages, which might obstruct full respiratory movement, should be permitted Abdominal distension, if present, should receive attention. Only in special circumstances will more drastic measures, such as bronchoscopy or bronchial suction, be required If these measures to deal with the mechanical factor result in rapid relief of symptoms and disappearance of physical and radiological signs, it is usually safe to discontinue the antibacterial treatment If, however, this happy result does not ensue, it may be assumed that infection by an invasive organism has occurred, and treatment similar to that suggested for apparently primary pneumonia is indicated.

Treatment in convalescence

Convalescence after pneumonia proceeds at a very variable pace. In a case of pneumococcal pneumonia of average severity, the patient may be allowed out of bed after the temperature has been normal for 7 days In cases of greater or less severity, longer or shorter periods of rest in bed are appropriate In pneumonias of the aspiration type, the patient should be allowed out of bed as

soon as the general condition permits. Breathing exercises will have been instituted in aspiration pneumonias therapeutically; during convalescence from acute specific pneumonias they are helpful in hastening the return of normal lung function, and should be started soon after defervescence.

After resolution appears clinically to be complete, it should be confirmed radiographically. In any case of apparently delayed resolution, the diagnosis should be carefully reviewed Loculated empyemas, bronchial new growths (both malignant and benign), foreign bodies, pre-existing bronchiectasis and *pulmonary tuberculosis should be considered in differential diagnosis, and* excluded, when necessary, by appropriate investigations before accepting the diagnosis of delayed resolution Nevertheless, resolution may exceptionally be delayed and yet eventually prove to be complete as long as 10 or 12 weeks after the beginning of the acute illness An adequate period of convalescence, the duration of which will depend upon the sort of life to which the patient has to return, should be enforced

BIBLIOGRAPHY

General

Bullowa, J G, M (1937) *The Management of the Pneumonias* New York; Oxford

— and Gleich, M (1938) "The aetiology, death rates and bacteremic incidence in the more frequent primary pneumonias of infants, children and adults" *Amer J med. Sci*, 196, 709

Medical Research Council (1951) "Treatment of clinical pneumonia with antibiotics" *Brit. med J*, 2, 1361.

Reimann, H A (1938). *The Pneumonias* Philadelphia, Saunders

Pneumococcal pneumonia

Blake, F G, and Cecil, R L. (1920) "Studies in experimental pneumonia" *J exp. Med*, 31, 403 and 445

Cecil, R L, Baldwin, H S, and Larsen, N P (1927) "Clinical and bacteriological studies of [illegible] *Arch intern Med* 40 253

[illegible]

med Ass, [illegible]

Fried, B M (1933) "Allergic lobar pneumonia" *J exp Med*, 57, 111.

Glynn, E E, and Digby, L. (1933) "Bacteriological and clinical observations on pneumonia and empyemata." *Med Res Coun. Spec Rep Ser*, No 79

[illegible] Robertson, O H (1934) "Physical signs and roentgenographic [illegible] 249

[illegible] circulation of the lung in [illegible]

[illegible] Untersuchungen uber die [illegible] en" *Z Hyg. Infektionskr*, 114, 659.

Gunn, F D, and Nungester, W J (1936) "Pathogenesis and histopathology of experimental pneumonia in rats." *Arch Path*, 21, 813

* Heffron, R (1939). *Pneumonia, with Special Reference to Pneumococcus Lobar Pneumonia*, New York; Commonwealth Fund

Humphrey, J. H, Joules, H, and van der Walt, E D (1948) "Pneumonia in N.W London 1942–44" *Thorax*, **3**, 112

Kline, B S, and Winternitz, M C (1915) "Inter vitam staining in experimental pneumonia and the circulation in the pneumonic lung" *J exp Med*, **21**, 311

Lindau, A (1933) "Studies on varying response to pneumococcal infections, especially pneumonia" *Acta path microbiol Scand*, **10**, 1

Permar, H H (1923) "Pathogenesis of experimental pneumonia in the rabbit" *J med Res*, **44**, 1.

Perry, C B (1934) "Peripheral circulation in acute lobar pneumonia" *Quart J Med*, **27**, 273

Rosenau, M J, Felton, L D, and Atwater, R M (1926) "An epidemiologic study of pneumonia and its mode of spread" *Amer J Hyg*, **6**, 463

Scott, T F, McN, and Finland, M (1934) "The cytology of pleural effusions in pneumonia" *Amer J med Sci*, **188**, 322

Sharp, E A, and Blake, F. G (1930) "Host factors in the pathogenesis of pneumococcus pneumonia" *J exp Med*, **52**, 501

Terrell, E E, Robertson, O H, and Coggeshall, L T (1933) "Experimental pneumococcus lobar pneumonia in the dog" *J clin Invest*, **12**, 393

Tilghman, R C, and Finland, M (1937) "Clinical significance of bacteremia in pneumococcic pneumonia" *Arch intern Med*, **59**, 602

Tillett, W S, and Francis, T (1929) "Cutaneous reactions to polysaccharides and proteins of pneumococcus in lobar pneumonia" *J exp Med*, **50**, 687

Haemolytic streptococcal pneumonia

Blake, F G, and Cecil, R L (1920) "Experimental streptococcus haemolyticus pneumonia in monkeys" *J exp Med*, **32**, 401

MacCallum, W G (1932) *Textbook of Pathology*, 5th ed, p 492 Philadelphia, Saunders

Miller, J L, and Lusk, F B (1918) "Epidemic of streptococcus pneumonia and empyema at Camp Dodge" *J Amer med Ass*, **71**, 702

Friedländer bacillus pneumonia

Belk, W P (1926) "Pulmonary infections by Friedländer's bacillus" *J infect Dis*, **38**, 115

Brock, R C (1946) "Studies in lung abscess" *Guy's Hosp Rep*, **95**, 40

Bullowa, G J M, Chess, J, and Friedman, N B (1937) "Pneumonia due to bacillus Friedlander" *Arch intern Med*, **60**, 735

Collins, L H (1936) "Chronic pulmonary infections due to Friedländer's bacillus, further observations" *Arch intern Med*, **58**, 235

— and Kornblum (1929) "Chronic pulmonary infection due to Friedlander's bacillus" *Arch intern Med*, **43**, 35

Grotts, B F (1949) "Pneumonia in infancy caused by Friedländer's bacillus" *J Pediat*, **34**, 174

Ritvo, M, and Martin, F (1949) "Clinical and Roentgen manifestations of Friedlander pneumonia" *Amer J Roentgenol*, **62**, 211

Solomon, S (1937) "Primary Friedlander pneumonia" *J Amer. med Ass*, **108**, 937

Staphylococcal pneumonia

Brock, R C (1945) "Studies in lung abscess" *Guy's Hosp Rep*, **94**, 115

Chickering, H T, and Park, J H (1919) "Staphylococcus aureus pneumonia" *J Amer med Ass*, **72**, 617

Kanof, A, Kramer, B, and Carnes, M (1934) "Staphylococcus pneumonia" *J Pediat*, **14**, 712

MacGregor, A R (1936) "Staphylococcal pneumonia" *Arch Dis Childh*, **11**, 195

MacKeith, R (1941) "Sulphathiazole in staphylococcal pneumonia" *Lancet*, **2**, 354

Reimann, H A (1933) "Staphylococcic pneumonia" *J Amer med Ass*, **101**, 514

piratory disease
32, 691

Brannan, D, and Goodpasture, E W. (1924). "Pathology of pneumonia caused by baci influenzae during an inter-epidemic period." *Arch intern. Med.*, 34, 739.

Bacillus anthracis pneumonia

Shennan, T, and Miller, J (1910). "Bronchial Anthrax." *J. Path. Bact*, 14, 556

Pneumonic plague

Bulstrode, H T (1911) "Suffolk outbreak of pneumonic plague." *Rep. Loc Govt. Bd Pi Hlth*, No. 52.

Wynn-Griffith, G. (1948) Pneumonic plague in Rangoon. *Lancet*, 1, 625.

Tularaemic pneumonia

Hunt, J S (1947) Tularemia . pneumonic forms *Ann intern. Med*, 26, 263

Parker, R T, Lister, L M., Bauer, R E, Hall, H E, and Woodward, T. E. (1950) "Use chloramphenicol in experimental and human tularemia" *J Amer. med Ass.*, 143, 7.

Post, R. B, Percefull, S. C., and Leming, H. E (1948) "Tularemia in the Ozarks region *J Amer med Ass*, 137, 352.

Stuart, B M, and Puffen, R. L (1945) "Tularemic pneumonia." *Amer J med Sci*, 210, 23

Woodward, T. E, Raby, W T, Eppes, W, Holbrook, W. A., and Hightower, J. A (1949 "Aureomycin in the treatment of experimental and human tularemia" *J Amer. me Ass*, 139, 830.

Tuberculous pneumonias

Brock, R C, Cann, R J, and Dickinson, J R (1937) "T ...
in childhood , secondary effects on th

Eliasberg, H, and Neuland, W. (1920) "
kulosen Sauglingen und Kinderh" *Jahrb Kinderh*, ...

Fish, R H, and Pagel, W (1938) "The morbid anatomy of epituberculosis" *J Path. Bact* 47, 593

Goldberg, B, and Gasul, B M (1930) Epituberculosis *Amer J. med Sci*, 180, 824

Kayne, G G, Pagel, W, and O'Shaughnessy, L (1948) *Pulmonary Tuberculosis*, 2nd ed London, Oxford

Reichle, H S. (1933) Resolving exudates in pulmonary tuberculosis of childhood *Amer J Dis Childh*, 45, 307 and 46, 969

Influenzal pneumonia

Scadding, J G (1937) Lung changes in influenza *Quart J Med*, 6, 425

Van Rooyen, C E, and Rhodes, A. J. (1948) *Virus Diseases of Man*, 2nd ed, New York Nelson.

Walshe, J M (1950) Fulminating staphylococcal pneumonia treated with massive doses of chloramphenicol and penicillin *Brit med J.*, 2, 1313

Pneumonia complicating measles

Box, C. R (1933) "On complications of specific fever, with special reference to scarlet fever and measles" *Lancet*, 1, 1271

Cole, R., and MacCallum, W G. (1919) "Pneumonia at a base hospital" *J Amer. med Ass*, 70, 1147

Ellison, J B (1931) "Pneumonia in measles" *Arch. Dis Childh*, 6, 37.

... *ed J*, 2, 1461.

... " *Medicine, Baltimore*, 21, 175

... *es of Man*, 2nd ed New York; Nelson

Wolins, W (1948) "Ornithosis (psittacosis), a review with a report of 8 cases resulting from contact with the domestic Pekin duck" *Amer J med Sci*, 216, 551.

Smallpox

Howat, H T, and Arnott, W M (1944) "Outbreak of pneumonia in smallpox contacts" *Lancet*, 2, 312.

Van Rooyen, C E, and Rhodes, A J (1948). *Virus Diseases of Man*, 2nd ed. New York; Nelson

* Contains comprehensive bibliographies

Chicken-pox
Claudy, W D (1947)
Waring, J
adults
Arch

Wechsler, H F, Rosenblum, A H, and Silk, C T (1946) "In... of an epidemic in an Army post." *Ann intern Med* 25, 113

Ass, J 53, 427 ... "Mucosal ...

Pneumonia presumed to be due to unidentified pneumonotropic virus
Adams, J M (1941) "Primary virus pneumonitis with cytoplasmic ... *med Ass*, 116, 925
— Green, R G, Evans, C A., and Beech, N (1942) "... rative study of two epidemics," *J Pediat*, 20, 405
* Breslow, L. (1945) "Epidemic of acute respiratory disease ... *J clin Invest*, 24, 775
Eaton M D ...

** R ...
Medicine, 26, 167 ... pneumonias, and ...
Scadding, J G (1948) "The pneumonias associated with ... *Lancet*, 1, 89
Verco, P. W (1949) "The radiology of primary atypical pneumonia ...

Rickettsial pneumonias
Q fever and Rickettsia burneti
Burnet, F M, and Freeman, M (1937), "Experimental ... *J Aust*, 2, 296
— — (1939) "Comparative study of rickettsial ... Montana (U S A) and from 'Q' fever" *Med J Aust* ...
Davis, G E, and Cox, H R (1938) "A filter passing ... *Publ Hlth Rep, Wash* 53, 2259.
Derrick E H (1937) "'Q' fever, a new fever entity ... tory investigation" *Med J. Aust*, 2, 281
Dyer, R E (1939) "Similarity of Australian 'Q' fever ... agent isolated from ticks in Montana" *Publ* ...

Laboratory infections
Committee on Acute Respiratory Diseases (1946), "A ... by the Balkan Grippe strain of Rickettsia burneti" ...
Hornibrook, J W, and Nelson, K R (1940) "An ... ciated with known non-bacterial agents: ... *Rep, Wash*, 55, 1936
Huebner, R J (1947) "Report of outbreak of ... Epidemiological features" *Amer J publ* ...

* Contains an account of an outbreak of respiratory ...
** Contains a full bibliography

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Lillie, R D, Perrin, T L, and Armstrong, C (1940). "Institutional outbreak of pneumonitis: histopathology in man and rhesus monkeys in pneumonitis due to virus of 'Q' fever." *Publ Hlth Rep, Wash*, 55, 149

Robbins, F C., and Rustigian, R (1946) "'Q' fever in Mediterranean area. report of its occurrence in allied troops: laboratory outbreak." *Amer. J Hyg.*, 44, 123.

"Q" fever in returning American troops, and evidence of rickettsial origin of "atypical pneumonia" in Mediterranean area.

Symposium (1946). "'Q' fever in the Mediterranean area report of its occurrence in allied troops" *Amer. J Hyg*, 44, 1-122

Evidence of rickettsial origin of "atypical pneumonia" in New Zealand troops in Mediterranean area.

Caughey, J. E, and Dudgeon, J A (1947) "'Q' fever. A serological investigation of a group of cases previously reported as atypical pneumonia" *Brit med J*, 2, 684

Outbreak among workers in a Texas cattle-yard

Symposium (1947) "'Q' fever in the United States" *J Amer. med. Ass*, 133, 813-821.

Q fever in England

Harman, J B (1949) "Q fever in Great Britain Clinical account of 8 cases." *Lancet*, 2, 1028

MacCallum, F. O., Marmion, B P, and Stoker, M G P (1949) "Q fever in Great Britain Isolation of cases of Rickettsia burneti from an indigenous case." *Lancet*, 2, 1027

Stoker, M G P (1949) "Serological evidence of Q fever in Great Britain" *Lancet*, 1, 178.

Whittick, J W (1950) "Necropsy findings in a case of Q fever in Britain" *Brit med J*, 1, 979

Aspiration pneumonia

Andrus, P. M. (1942) "Silent broncho-pneumonia" *Canad. med. Ass, J.*, 47, 339.

Becker, R. P. (1943). "Pneumonia complicating mild respiratory infections." *Canad med Ass. J*, 48, 324

Belcher, J R (1949) "The pulmonary complications of dysphagia" *Thorax*, 4, 44

[illegible] London Oxford [illegible]

[illegible] *Lancet*, 1, [illegible]

Wraith, D. G (1951) "Minor respiratory infections" *Brit J Tuberc.*, 45, 15

* This contains a bibliography up to 1939

bon monoxide poisoning resulting from bombing and fires (Fridlyand, 1947) e were 87 cases of pneumonia (34 per cent) out of a total of 256 hospital cases eater percentage of the more severely gassed cases developed pneumonia sphyxiants and centrally acting poisons producing anaesthesia, such as trichthylene and other volatile solvents, do not give rise to pneumonia except by ration There is no evidence of any direct effect on the lungs by the more portant members of this group, but their effects on other organs are varied ones, 1951) There is no evidence of an increased incidence of pneumonia or spiratory infections during the manufacture of trichlorethylene in workers onstantly exposed to small concentrations Smoking is not allowed during work ecause there is danger of decomposition with the production of phosgene

Few cases of pneumonia are recorded from exposure to carbon tetrachloride. Hamilton and Johnstone (1945) report a fatal case after 2½ hours exposure in a large well-ventilated machine room in January, 1941 Symptoms of poisoning involving the digestive tract, liver and kidneys are recorded Exposure to low concentrations of hydrogen sulphide causes conjunctivitis and mild irritation of the upper respiratory tract, but pneumonia is not a sequel Ahlborg (1948) describes 100 cases occurring in 5 years and in no case were there signs of pulmonary oedema Pulmonary oedema may follow exposure to high concentrations of methyl bromide, which is used in refrigerators and in fire extinguishers

Various barbiturates are now widely used and acute poisoning may result from suicidal or accidental overdosage Coma is a feature of poisoning with small reacting pupils, flaccid limbs and sometimes an extensor plantar response. Death occurs from respiratory failure which is accompanied by pulmonary oedema and bronchopneumonia if the patient survives 1–2 days

LUNG IRRITANT GASES

Workers in industry are exposed to a number of irritating gases, but serious effects are uncommon Those gases that affect the lungs do so as part of an acute illness and chronic effects are rare, but it must be stated that only recently have the consequences of chronic exposure to irritant gases and dusts been studied

Ammonia and sulphur dioxide, hydrochloric and other acids cause irritation of the eyes, mouth and larynx, substernal pain, respiratory spasm and a distressing cough Chlorine and other halogens also cause immediate symptoms, but in addition they produce irritation of the finer bronchi and more rarely the lungs With adequate treatment recovery occurs in a few hours, although laryngitis and bronchitis may persist for a few days Burns of the face, pharynx and bronchi may rarely occur following exposure to high concentrations of acid gases and ammonia Radiological changes are usually slight and include pulmonary congestion and occasionally opacities in the lower and mid-zones The changes rapidly clear

During the years 1932–48, 820 cases of chlorine gassing in workers on chemical processes had been observed by the writer and his colleagues Of these, 728 were classified as mild, they reported to the medical department with a painful cough and increased respiration Considerable respiratory embarrassment was present in 81 with distended cervical veins and some cyanosis, and 11 were sent home after treatment The pulse and respiratory rates were raised and the physical signs were those of bronchitis, medium rhonchi and râles being present on ausculta-

tion of the chest. Nine cases were severe and required admission to hospital, but even in these cases pulmonary oedema or pneumonia did not ensue It is probable that in World War 1 oedema and pneumonia ascribed to chlorine were due to mixtures of chlorine and phosgene There is, however, other evidence both clinical and experimental, reporting pneumonia [illegible]

[illegible]

damage A study of death certificates and sickness absenteeism shows no excessive tendency towards the development of chronic bronchitis or emphysema

Gilchrist and Matz (1933) have made a study of the histories of 96 men gassed with chlorine Nine of these men had symptoms attributable to gassing, 7 had doubtful symptoms and 80 had none Of the 9 positive cases, 5 had tuberculosis (3 with co-existing emphysema) and 3 had chronic bronchitis (1 with emphysema) A clinical and radiological survey made, by the writer, of other men exposed constantly for 20 years or more to small concentrations of hydrochloric and sulphuric acids, ammonia and sulphur dioxide, does not reveal any evidence of *pulmonary damage*

Nitrous fumes may be encountered not only as the result of incomplete detona- [illegible]

encountered as the result of accidents in industry The fumes have a reddish brown colour and consist of a mixture of nitric oxide and nitrogen peroxide Exposure to nitrous fumes, nickel carbonyl and phosgene causes less irritation of the upper respiratory tract and the initial symptoms are often slight The patient may be quite free from symptoms an hour after gassing and considerable difficulty may be experienced foretelling the possibility of complications. Pulmonary oedema may arise suddenly, the patient becoming restless, pale and collapsed The complexion is "leaden grey," the skin clammy, and the pulse rapid and weak Cough is associated with copious watery expectoration and there is a raised respiratory rate The production of pulmonary oedema after a latent period is an extraordinary development (Fig 40) Some damage must occur to the capillary endothelium and alveolar walls, but this is certainly not irreparable Many factors may be involved, engorgement of the lungs with blood, dilatation of capillaries with increased permeability, interference with lymphatic drainage, liberation of histamine

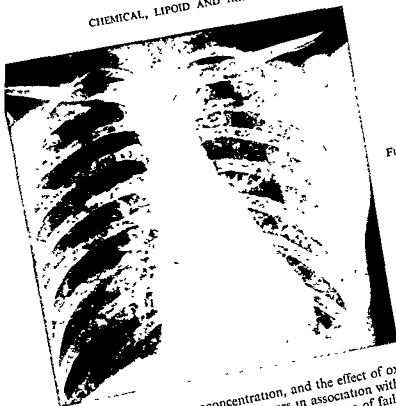


FIG 40—Pulmonary oedema resulting from exposure to phosgene.

by damaged lung, haemoconcentration, and the effect of oxygen deficiency on the heart A similar clinical picture occurs in association with hypertension which is considered by most clinicians to be a manifestation of failure of the left ventricle. A great deal of experimental work has been done by Cameron (1946), who concludes that mechanical anoxia arises from the tremendous outpouring of fluid, rich in plasma proteins, into the voluminous air spaces of the lungs Bronchial constriction may add to the anoxia Existing evidence shows that phosgene as such is not absorbed into the blood from the air spaces, so that it does not contribute to the problem through its inherent chemical properties It is unlikely that it produces hydrochloric acid in the alveoli and possible that some effect on the respiratory centre occurs

The development of pulmonary oedema following exposure to phosgene causes a desperate medical emergency and 6 cases have been successfully treated and personally observed since 1936, 1 case succumbed In surviving patients recovery is apparently complete and there is no permanent damage to the lungs as shown by sickness records, clinical and radiological examination

Treatment of gassing by lung irritants

Emergency treatment should include the removal of contaminated clothing ar keeping the patient warm and at rest Some relief from the distressing irritati of the upper respiratory tract can be obtained from the inhalation of a stea atmosphere from a bronchitis kettle or from a vessel containing two teaspoonf of Friars' balsam in a quart of hot water Difficulty in breathing or cyan

should be relieved by the administration of oxygen and carbon dioxide, or oxygen, through a B L B or similar mask In chlorine gassing the desire to cough can also be relieved by the administration of one teaspoonful of the Camphorated Linctus of Diamorphine (*B P C*, 1934) or of the Elixir of Terpin Hydrate with Ethylmorphine Hydrochloride (*B P C*, 1934)

In severe cases of phosgene gassing oxygen has been given directly for several days with a reducing valve and simple flowmeter (Fig 41) Hardy and Barach (1945) recommend that oxygen should be breathed with a positive expiratory pressure of 4 centimetres of water, and this has appeared effective in personal trials.

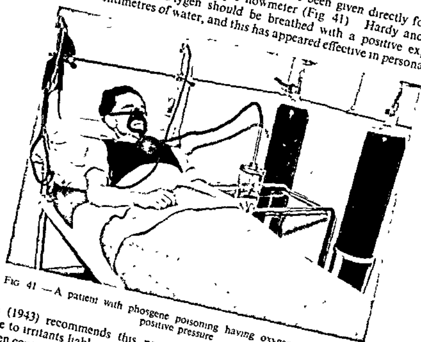


Fig 41 —A patient with phosgene poisoning having oxygen therapy under positive pressure

Carlisle (1943) recommends this procedure in patients suspected of sufficient exposure to irritants liable to produce pulmonary oedema Although oxygen has been given continuously for periods of 24–48 hours in many cases without ill effects, it seems unwise to maintain 100 per cent concentration for longer than 12 hours Comroe and his colleagues (1945) have reported substernal pain and fall in vital capacity, and the effects of increased oxygen, carbon dioxide and nitrogen pressures are discussed by Stadie, Riggs and Haugaard (1944) and Bean (1945) The administration of oxygen is by far the most important measure of treatment and other remedies are of doubtful value Atomized solutions of 10 per cent sodium thiosulphate have proved disappointing for the treatment of chlorine gassing Epinephrine to relieve bronchial spasm and calcium to reduce permeability of the capillaries, and Mersalyl (*B P*) to promote excretion are not noticeably effective

Courtice and Foss (1946) and others have indicated on experimental evidence that concentrated and normal serum and plasma have deleterious rather than beneficial effects Hexamine by the oral or intravenous route protects animals

ainst the effects of phosgene, but it does not prevent death or affect haemoconcentration if given after exposure

Venesection should be practised for embarrassment of the right heart and not or cyanosis alone Morphine should not be given. Nikethamide has been of value in some cases.

BERYLLIUM

Beryllium is a light metal which, because of the strength and useful properties of its alloys, is being used on an increasing scale It is also used in the field of atomic energy and for coating the tubes of fluorescent strip lamps.

Exposure to beryllium and its compounds, particularly the oxide, may cause a general disease with pulmonary symptoms and major pathological changes in the lungs Symptoms have been reported following slight or intermittent exposure to minute quantities of beryllium and even after the inhalation of dust from workers' clothes Acute symptoms may arise at work : conjunctivitis, nasopharyngitis and tracheo-bronchitis occur, as well as dermatitis and granulomatous lesions in the subcutaneous tissues An excellent account of the acute pneumonitis and pulmonary granulomatosis of beryllium workers is given by Machle, Beyer and Gregorius (1948), although van Ordstrand, Hughes and Carmody reported acute cases in 1943

Acute, subacute and chronic forms of the illness have been described In the acute disease a diffuse pneumonitis occurs with alveolar exudates consisting of macrophages, oedema fluid and fibrin Lymphocytes and plasma cells are seen in the lung spaces and there is marked fibroblastic proliferation in 1–2 weeks The absence of necrosis and polymorphs is noteworthy In cases of chronic disease scattered nodules, diffuse fibrosis, and emphysema resemble the changes of sarcoidosis. Granulomas are present in the lungs, skin, lymph nodes and liver. Beryllium can be detected in the urine, blood and tissue by spectrographic analysis The symptoms of acute illness are cough with streaking of the sputum, but little pyrexia , dyspnoea and cyanosis may be marked, and when the lower respiratory tract is affected tachycardia and rapid loss of weight occur. Scattered râles are present on auscultation of the chest Some progression of the illness occurs over 2–3 weeks when commonly resolution begins and full recovery occurs in 2–5 months Subacute cases complain of fatigue, mild dyspnoea and loss of weight but can continue at work. Chronic disease may arise after a delay of a few months, but has been reported 2 years following acute symptoms and several years after exposure. Constitutional symptoms such as weakness, anorexia and loss of weight associated with a cough are present before abnormal signs can be detected in the lungs Dyspnoea is often severe and is aggravated by the onset of cardiac failure The diagnosis can be confirmed by the presence of granulomatous changes and beryllium in sections of liver obtained by puncture Considerable work has been done in studying the reported cases and intoxication in animals, but the significance of changes in the blood chemistry, particularly the calcium and phosphorus and alkaline phosphatase, is not yet assessed Of the cases at present reported death occurs in about one third from right-sided heart failure, intercurrent infection in the lungs and cachexia, and another third suffer permanent disability from pulmonary fibrosis and emphysema Radiological changes in the lungs are precede

by clinical signs by 2–3 weeks The appearances resemble pulmonary congestion with increased linear markings and ground-glass granularity throughout the lung fields Bronchial or lobar consolidation may occur with enlarged hilar shadows (Fig 42) With clinical improvement the skiagrams may show nodules gradually clearing over 1–4 months Even slight changes in the skiagrams associated with mild

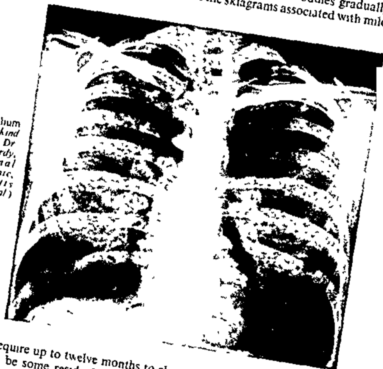


Fig 42.—Beryllium sarcoid (*By kind permission of Dr Harriet L Hardy, Occupational Medical Clinic, Massachusetts General Hospital*)

acute illness may require up to twelve months to clear completely (Aub and Grier, 1949) There may be some residual fibrosis with emphysema, and spontaneous pneumothorax may develop Tuberculosis must be carefully considered as a possible diagnosis The generally accepted criteria of sarcoidosis are not compatible with the severe respiratory disability, poor prognosis and absence of radiological changes in the bones

Treatment

The importance of complete rest is stressed. No specific therapeutic agent of value has yet been reported and treatment is symptomatic The value of ACTH and cortisone is not yet assessed, but improvement in the x-ray appearance has occurred following their use

Complete bed rest and a long period of convalescence are advisable as deaths have occurred from a return of the pulmonary oedema on resuming activity

The disease can be prevented by plant control, protective clothing and medical examination of workers including x-ray examination of the chest

MANGANESE

Considering the widespread use of manganese compounds poisoning is a rarity. Symptoms arise from the inhalation of manganese dioxide dust or fumes, or from the fusing of manganese steel A history of 1–3 years exposure is usual, but cases are recorded after 3 months exposure to excessive amounts of dust Slight absorption may occur through the skin and elimination occurs mainly in the faeces but also in the urine Gliosis is produced in the basal ganglia with symptoms resembling Parkinson's disease

In 1921 Brezina first drew attention to the relationship of manganese to pneumonia , he reported that 5 out of 10 men working in a pyrolusite mill had died of pneumonia in a period of 2 years Baader (1932) ascribed the high incidence of pneumonia among workers making dry battery cells to manganese ; while Elstad (1939) observed that the erection of an electrical plant for manganese smelting in Sauda in Norway was followed by a tenfold increase in the mortality rate for pneumonia in that area Men exposed to the inhalation of manganese dioxide dust and the higher oxides of manganese suffer from nasopharyngitis, tracheitis and bronchitis The symptoms are probably due to oedema of the respiratory epithelium and are sometimes associated with bronchial spasm Lloyd Davies (1946) observed that men employed in the manufacture of potassium permanganate who were exposed to manganese dioxide dust have an incidence of pneumonia of between 15 and 63 per thousand compared with an average of 0 73 in all other male workers of the same firm Permanent damage and fibrosis are not apparently sequelae of exposure Animal experiments support the view that the inhalation of manganese dust produces irritation in the lungs In mice an intense mononuclear proliferation and infiltration of the lung tissue leads to cell destruction

Poisoning can be prevented by the control of dust and fumes in enclosed processes, the use of mechanical conveyors, wet drilling and adequate exhaust ventilation No specific treatment is known

VANADIUM

Vanadium is used in the making of high grade steel and also as a catalyst in chemical processes Dutton (1911) described symptoms attributed to exposure to vanadium ore In widespread toxic effects he includes an irritating cough and haemoptysis Wyers (1946) has reviewed the literature and described his observations of 50–90 workers over a period of 9 years The unusual combination of dust reticulation and systemic intoxication occurs after exposure to vanadium pentoxide The main clinical feature is acute irritation of the respiratory tract Symptoms are paroxysmal cough, rarely with haemoptysis, dyspnoea, and pains in the chest A barrel shaped chest, bronchospasm and bronchitis are noted Allergic skin lesions occur It seems likely that colds and pneumonia are of more frequent occurrence than in the general population.

These cases and others in the literature (Fairhall, 1946), as well as the results o animal experiments prove that vanadium is toxic and irritant and will produce acu and chronic pulmonary disease

An increased content of vanadium in the blood and urine can be demonstrated in affected workers by spectroscopic analysis (Sjöberg, 1950).

Treatment is symptomatic. The use of BAL is under review. The toxic symptoms can be prevented by the elimination of dust by exhaust ventilation and protective masks.

CADMIUM AND CHROMIC ACID

Cadmium fume sometimes arises in considerable density in fires. Spolyer, Keppler and Porter (1944) reviewed the literature on the subject and showed that the usual symptoms were chills, irritation of the throat, cough with purulent sputum, pain in the chest, dyspnoea, vomiting, headache and dizziness. Necropsies in fatal cases have shown extensive haemorrhagic oedema of the lungs and animal experiments have also shown severe pulmonary damage.

Meyers (1950) reviewed the literature on the effects of chromic acid on the lungs and reported 2 cases in which acute pulmonary lesions developed characterized by cough with purulent sputum, dyspnoea and severe chest pain. The radiological changes were slight.

OSMIC ACID

Osmium metal or the alloy osmiridium is not toxic, but osmic acid (osmium tetroxide) is volatile and highly irritating. Immediate symptoms are due to irritation and include smarting of the eyes with lachrimation and haloes, headache and inability to breathe. McLaughlin, Milton and Perry (1946) have reviewed the literature and recorded the effects of osmium tetroxide in seven men. There were irritative effects and one man complained of cough and expectoration following exposure, but no chronic or cumulative effects were noted. Capillary bronchitis and broncho-pneumonia have been reported in rabbits following exposure, and Raymond (1874) describes the only fatal case in the literature. In most of the cases reported, symptoms subsided within 24 hours and did not require treatment.

LIPOID PNEUMONIA

Lipoid pneumonia, which is a chronic pulmonary consolidation caused by mineral, animal or vegetable oils or fats entering the lung, was first described by Laughlen in 1925. Histologically the consolidation is found to be a foreign body reaction, the oils and fatty acids formed by hydrolysis act as irritants and stimulate the surrounding lung to form fibrous tissue with giant cells and accumulations of macrophages.

The condition arises in infants and children from the aspiration of milk, vitamin oils and cod liver oil, and occurs in about 5 per cent of children dying from all causes. Heacock (1949) describes 68 cases of pneumonia in 156 children admitted to hospital suffering from the effects of swallowing kerosene. In children and adults there is usually associated impairment of the cough reflex or difficulty in swallowing. Adults develop the condition from the inhalation of mineral oil or nasal drops (Freiman, Engelman and Merrit, 1940). Liquid paraffin taken as a laxative is perhaps the commonest cause of the condition, Volk and his colleagues (1951) attributed half the incidence to this cause. These authors showed that the condition was relatively common in the chronic sick; among 389 sick patients the

found it in no less than 57, of whom half suffered from Parkinson's disease, the others had diseases such as disseminated sclerosis, cerebral palsy, arthritis and hypertension Oil enters the alveoli and interstitial tissue especially at the base The symptoms are fever, cough with sputum Skiagrams show consolidation at the base, especially the right (Fig 43) In long standing cases fibrosis and bronchiectasis are described subsequent to irritation of the pulmonary epithelium (Paterson, 1938)

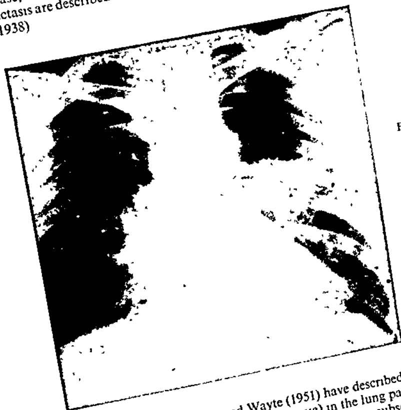


Fig 43. — Lipoid pneumonia of industrial origin, caused by the explosion of a tank containing fat (*By courtesy of Dr. A C. C Hughes Chester*)

De Navasquez, Trounce and Wayte (1951) have described pneumonic consolidation due to fatty deposits (lipoid pneumonia) in the lung parenchyma adjacent to a carcinoma treated by deep radiotherapy They subsequently observed the condition in 4 other patients with lung carcinoma who had not been treated by irradiation The histological picture was similar to an inhalation lipoid pneumonia, and chemical analysis showed the oily droplets to be composed of cholesterol esters This finding of endogenous lipoid suggests that it arose from degeneration of the patient's own tissues These findings indicate also that the differential diagnosis between lipoid pneumonia and carcinoma may sometimes be difficult Investigations may include the examination of sputum for lipoid and a similar examination of exudate from needling of the lung Clearly it will in some instances be impossible with a routine x-ray examination to differentiate between lipoid pneumonia and bronchogenic carcinoma

Groover, T A , Christie, A C., and Merritt, E A (1923) " Intrathoracic changes following roentgen treatment of breast carcinoma " *Amer J. Roentgenol* , **10**, 471–476.
Hamilton, Alice, and Johnstone, R. T. (1945) *Industrial Toxicology*. Ed by H A. Christian

Radiology, **53**, 793.
Jones, A T , and Chamberlain, E N (1951) " Occupational diseases and toxicology " In *Textbook of Medicine* Ed by Chamberlain, E N Bristol ; Wright
Kaplan, I I , and Etkin, S. I (1948) " Trea
multiple post technic simulating rotation th
Kooperstein, S I , and Bass, H. E (1946)
instillation of Lipiodol in bronchial asthma
Laughlen, G F (1925). " Studies of pneumonia following nasal pharyngeal injections of oil " *Amer J. Path* , **1**, 407
Lloyd Davies, T A (1946) " Manganese pneumonitis " *Brit J. industr Med* , **3**, 111.
Machle, W , Beyer, E C , and Gregorius, F (1948) " Berylliosis acute pneumonitis and pulmonary granulomatosis of beryllium workers." *Occup Med*, **5**, 671

Meyers, J B (1950) " Acute pulmonary complications following inhalation of chromic acid

Raymond, C (1874) " Empoisonment par l'acide osmique " *Pr méd* , **2**, 373
Robertson, P W , and Morle, K. D F (1951) " Delayed pulmonary complications of bronchography " *Lancet*, **1**, 387
Shanks, S C , and Kerley, P (1951). *A Text Book of X-ray Diagnosis by British Authors*, p 372–3, Vol 2, 2nd Ed. London , Lewis
Shiels, D O , and Robertson, I (1946) " Poisoning of firemen by irritant fumes , cadmium and sulphonated castor oil " *Brit J industr Med* , **3**, 213
Sjöberg, Sven-Gosta (1950) " Vanadium pentoxide dust " *Acta med scand* , Suppl 238
Spolyar, L. W , Keppler, J F , and Porter, H G (1944) " Cadmium poisoning in industry." *J industr Hyg* , **26**, 232
Stadie, W C , Riggs, B C., and Haugaard, N (1944) " Oxygen poisoning " *Amer J med Sci* , **207**, 84
Volk, B W , Nathanson, L , Losner, S , Slade, W R , and Jacobi, M (1951) " Incidence of lipoid pneumonia in survey of 389 chronically ill patients " *Amer J med* , **10**, 316
Warren, S , and Gates, O (1940) " Radiation pneumonitis , experimental and pathologic observations " *Arch Path* , **30**, 440
Warren, S , and Spencer, J (1940) " Radiation reaction in the lung " *Amer J Roentgenol* , **43**, 682–701
Widmann, B P (1942) " Irradiation pulmonary fibrosis " *Amer J Roentgenol* **47**, 24–36
Winternitz, M C (1920) *Pathology of War Gas Poisoning* New Haven , Yale University Press.
Wyers, H (1946) " Some toxic effects of vanadium pentoxide " *Brit J. industr. med* , **3**, 177.

CHAPTER 7

WHOOPING-COUGH

KENNETH M. A. PERRY

AETIOLOGY

Bacteriology

WHOOPING-COUGH, which is also known as pertussis, is an infectious disease caused by a small Gram-negative bacillus, *Haemophilus pertussis*, the bacillus of Bordet and Gengou Milder cases result from an allied bacillus, *H. parapertussis*. They are minute bacilli closely related to the influenza group. They are difficult to grow, but can be cultivated most readily on a horse blood-potato medium known as Bordet-Gengou medium, at 37°C

Epidemiology

The disease is the most serious and fatal of the infectious diseases which affect children in the British Isles During the past 10 years the fatalities in England and Wales have varied between 700 and 2,400 a year, two-thirds of the number of deaths occur under the age of 1 year

In 1942 the low mortality figure of 79 deaths per million children under 15 was recorded by the Registrar-General In 1943 the figure was 91 but since this time the mortality rate has fallen rapidly as is shown by the notifications and deaths in the London County Council area

TABLE

NOTIFICATION AND DEATH RATE OF WHOOPING-COUGH IN THE LONDON COUNTY COUNCIL AREA

	Notifications	Deaths	Case fatality per cent
1940	669	10	1·49
1941	7,944	111	1·40
1942	6,234	101	1·62
1943	6,661	84	1·26
1944	7,136	116	1·63
1945	3,264	47	1·44
1946	6,887	53	0·77
1947	9,267	83	0·89
1948	10,450	55	0·53
1949	5,754	27	0·47
1950	10,875	30	0·27

Pertussis is essentially a disease of temperate climates, being rare and less severe in the tropics The disease may occur at any time of the year, but the maximal incidence is in winter and spring (Fig 44) It occurs in epidemics but between the epidemics it is always endemic. The disease is more prevalent in cities and industrial areas than in rural districts Epidemics with high mortality tend to occur in cycles of 7–10 years in isolated communities. Whooping-cough may occur at any age, but new-born infants are particularly susceptible Most

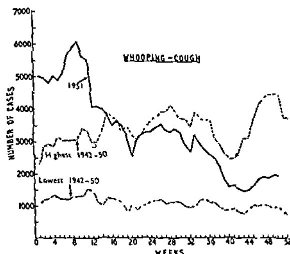


Fig 44 —Graph showing the incidence of whooping-cough in England and Wales from 1942 to 1951 (*By courtesy of the Editor of the British Medical Journal*)

children are born with circulating antibodies, but these quickly disappear More than 50 per cent of the children in England have had the disease before they go to school After the age of 5 years, its incidence gets progressively less, but it is sometimes seen in the elderly, even over the age of 70 years. It is slightly more common in females than in males Whooping-cough has frequently been observed to follow an attack of measles Second attacks are so extremely rare as to be considered for practical purposes non-existent ; abortive attacks occur

The incubation period is uncertain, but patients should be isolated for 5 weeks from the commencement of the whoop, while non-immune contacts should be isolated for 3 weeks

PATHOLOGY

[illegible]

infiltration of this area by polymorphonuclear leucocytes In the lung itself there

develops vesicular and interstitial emphysema as well as patchy areas of collapse. There is peribronchial and peribronchiolar infiltration, and this peribronchial cellular reaction extends from the hilum along the bronchial rays to the middle or outer zone of the lung. In more advanced cases, there is a typical interstitial pneumonia with thickening of the alveolar walls and infiltration with monocytes. Collapse of areas of lung results from the blockage of bronchioles with catarrhal [illegible]

Capillary haemorrhages and oedema are sometimes found in the brain and meninges.

CLINICAL COURSE

Catarrhal stage

The disease is characterized by catarrh of the respiratory tract and by periodical recurrent laryngeal spasms of a distinctive type, known as a "whoop". The first stage is a catarrhal condition which usually lasts for about 2 weeks. The child is febrile and tends to have a running nose and troublesome cough, there is little to distinguish it from catarrhal bronchitis, so that diagnosis at this stage is not possible unless the patient is known to have been exposed to the infection. Towards the end of this period the cough tends to assume a paroxysmal character and is particularly severe at night, hence resulting in loss of sleep. Sneezing sometimes occurs. The cough causes congestion of the head and neck, and frequently finishes with retching and vomiting. Spikes of fever occur as a result of the infection of areas of collapsed lung, resulting from the pressure of the mediastinal glands on the s[illegible]
under the age of 5 years), or [illegible]
by the tenacious sputum whi[illegible]

Paroxysmal stage

The paroxysmal stage is quite distinctive, the bouts of whooping occurring often in quick succession but sometimes with long periods of freedom. They may occur suddenly as a result of external stimuli such as excitement, draughts or a meal. A short inspiration is followed by a rapid succession of coughs, which cause the child to become cyanosed. The veins of the head and neck become engorged, the mouth is frequently open with the tongue protruding, the eyeballs become prominent and the skin is bathed in perspiration. The spasm ends suddenly, with a relaxation of the laryngeal spasm and the occurrence of the whoop, caused by the long ensuing inspiration. Severe attacks leave the child exhausted. During the attack droplets of viscid mucus, which are sometimes blood-stained, are expectorated. In young children convulsions sometimes occur. Epistaxis and sub-conjunctival haemorrhages are also known and sometimes the ear-drum is punctured. The paroxysmal stage may last up to 10 weeks, [illegible] winter catarrhal [illegible] arkedly [illegible] hild an easy prey to other infections.

On examination there are frequently many fine crepitations at the bases, but

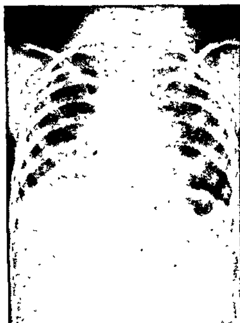


FIG 45—Skiagram of the chest in whooping-cough, showing enlargement of mediastinal glands and patches of collapse.



FIG 46—Skiagram of the chest of a child aged 4, showing a right sided tension pneumothorax complicating whooping-cough

re are no other distinctive signs in the lungs. Sometimes there will be a allow ulcer on the under surface of the tongue, caused by its protrusion over e lower incisor teeth during the spasms of coughing.

adiographic and laboratory findings

Skiagrams of the chest may show enlargement of the mediastinal glands r areas of collapse (Fig 45) The blood count is characteristic even in the early catarrhal stage, with an absolute lymphocytosis The white cells may be 25,000 or more per cubic millimetre, of which 70 per cent are lymphocytes. The bacillus can be cultivated either from per-nasal or laryngeal swabs, or by inoculation of Bordet-Gengou culture media in a Petri dish, which is held 6 inches from the mouth during a spasm of coughing The media consists of defibrinated blood agar containing penicillin The growth is often recognizable in about 2 days

COMPLICATIONS

Secondary infection with staphylococci, streptococci, pneumococci or Friedlander's bacillus, in the areas of collapse, often gives rise to pneumonia. Spontaneous pneumothorax may result from rupture of the lung during a bout of coughing (Fig 46) This occurrence is most common in infants and it may prove fatal, particularly if it is not recognized Bronchiectasis is, perhaps, the most important late complication of the disease (Lees, 1950)

The suggestion that whooping-cough and tuberculosis commonly occur together has been made in the literature, but there is little evidence that there is any connexion between the two diseases Haemorrhages resulting from the mechanical strain of coughing occur, but are not commonly serious, however cerebral haemorrhages and detachment of the retina have been known

Hernia and prolapse of the rectum are occasionally produced in young children

Convulsions, coma, paralysis, aphasia, paralysis of the ocular muscles, and defects of sight, hearing and intelligence have been attributed to whooping-cough.

TREATMENT

General measures

When the diagnosis is made isolation should be enforced Fresh air and free ventilation are of the greatest value, but unfortunately the disease frequently occurs in wet damp winter weather, when it is essential to keep the patient in a relatively uniform temperature indoors, so as to avoid secondary acute respiratory infections During the attack of whooping, the patient should be supported and the clothing should be loosened Expectoration and vomit should be disposed of in a suitable receptacle The lips should be wiped dry after the attack The diet should be light and digestible, and anything which induces coughing should be avoided.

Specific treatment

Chloromycetin is bacteriostatic to *Haemophilus pertussis* and is the most effective drug in the treatment of the disease, although its action is rarely dramatic (Gray, 1950a and b, Macrae, 1950, Lassen and Grandjean, 1951) It should be started as early in the disease as possible and preferably before the twelfth day.

A 10-day course is indicated and the antibiotic should be given at 6-hourly intervals as a sweetened powder The dosage for children under 1 year of age is 1 gramme a day, up to 3 years, 1·5 grammes, up to 10 years, 2 grammes.

Aureomycin, in a dosage of 350 milligrams per kilogram of body-weight per 24 hours for 8–10 days, was found by Miller and Ross (1950) to improve the patients' condition, so that they were free from paroxysms in 7–10 days

Terramycin has been used in a daily dosage of 100 milligrams per kilogram of body-weight for 10 days Jackson, Finland and others (1950), noted its beneficial effect and Booker, Farrell and West (1951) reported its use in 41 cases They found that the fall in temperature was rapid and the toxaemia greatly reduced The efficacy of the drug is similar to Chloromycetin

Wannamaker, Kohn and Weichsel (1949) showed that streptomycin, seemed to influence the course of the disease favourably , it was given as an aerosol and by intramuscular injections of 0 05 gramme 3-hourly to infants under 3 months of age, of 0 1 gramme to children from 3 months to 3 years, and from 0 1 to 0 2 gramme 3-hourly to older children, the treatment continuing for 6 days

Symptomatic treatment

The spasms of coughing may be treated with antispasmodics and sedatives Phenobarbitone is as effective a sedative as any, the dosage for infants being ⅛ grain thrice daily, and ½ drachm of Elixir Phenobarbitoni (*B P C*) being convenient. Bromoform, in drops (1 for each year of age up to 6) or as Elixir Bromoformi (½–2 drachms), is useful Atropine is the best antispasmodic Tincture of belladonna (5–15 minims) may be used in an attempt to relax the spasm. Atropine methyl nitrate (Eumydrin) in a 0 6 per cent alcoholic solution may be given in doses of 4–8 drops 4-hourly Ephedrine (⅛ grain for infants and 8½ grains for children up to 5 years) in a simple linctus is also a good antispasmodic, and is given 3 times a day Intramuscular injections of ether, in doses of 1–2 millilitres every 2 days, sometimes reduce the number of paroxysms After the fourth week, when the sputum is especially viscid, expectorants are of some value, the best being potassium iodide, given every 4 hours in a mixture such as

Potassium iodide	3 gr
Ammonium carbonate	3 gr
Potassium bicarbonate	10 gr
Camphor water to	1 fluid oz

Real or imitated high altitudes —At the Park Hospital in London, treatment has been attempted by using a decompression chamber for 45 minutes after the third week of the disease (Banks, 1951) It is equivalent to the atmospheric pressure at 12,000 feet Odegard (1946), however, thought that altitude-flying treatment was of doubtful value, and Harpoth (1949) thinks that the effect is mainly psychological, although the stimulation of deep breathing by oxygen lack, as well as radiation effects at 10,000 feet, may produce benefit

Treatment of complications

Owing to the seriousness of bronchiectasis as a late complication of the disease, determined efforts should always be made to re-expand any area of collapse, which may be observed Postural drainage is often successful but in some instances bronchoscopy may be necessary

PREVENTION

Isolation of patients

A child with whooping-cough should always be isolated and never allowed to come into contact with young children, particularly infants It is most important that no new-born child should be allowed to come in contact with any person known to be suffering from the disease. There is reason to believe that a patient ceases to be infectious after 5 weeks, because after that time it is no longer possible to recover *Haemophilus pertussis* from the sputum Return to school in uncomplicated cases is, therefore, permissible at this stage

Immunization

Good pertussis vaccines certainly appear to reduce the incidence of whooping-cough, and inoculated persons who develop the disease usually get a milder attack. Trials carried out by the Medical Research Council (1951), on 7,558 children between 6 and 18 months of age, showed that pertussis developed in 149 among 3,801 vaccinated children whereas there were 687 cases among 3,757 who were unvaccinated The corresponding attack rates per 1,000 child-months of observation were 1·45 and 6 72, giving a reduction in the incidence of the disease of 78 per cent Among children exposed to pertussis in their own homes the attack rates were 18 2 per cent in the vaccinated and 87·3 per cent in the unvaccinated groups

There is, however, considerable variation in the potency of these preparations; those prepared according to the method of the Michigan Department of Health appear to give a considerably greater degree of protection than do the others

Immunization may be carried out at any time after the age of 2 months, but if the patient is immunized at a young age it is wise to give a second injection after an interval of a year It is best avoided during the latter half of the year, owing to the prevalence of poliomyelitis A total dose of 100,000 millions of organisms, given in 3 injections at monthly intervals, is that usually recommended; different vaccines have a strength varying between 15,000 and 50,000 millions of organisms per millilitre This can be combined with diphtheria prophylactic

It should be stressed that chemotherapeutic substances are only effective in the early stages of whooping-cough when it is difficult to diagnose and therefore, even more than in most diseases, prophylaxis is the best form of treatment

BIBLIOGRAPHY

Banks, H S (1951) "Whooping cough" *Brit. med J*, **1**, 689

Booker, C E, Farrell, J B, and West, E J (1951) "Pertussis clinical comparison of t newer antibiotics" *J Pediat*, **38**, 411

Gallavan, M, and Goodpasture, E W (1937) "Infection of chick embryo with H pertu reproducing pulmonary lesions of whooping cough" *Amer J Path*, **13**, 1927

Gray, J D (1950a). "Observations on chloramphenicol" *Lancet*, **1**, 150

— (1950b) "Aureomycin and chloramphenicol in whooping cough" *Ibid*, **2**, 800

Harpoth, H (1949) "Treatment of whooping cough by means of altitude flying and de pression" *Nord Med*, **41**, 164.

Jackson, G G, Chang, S, Barnes, M W, and Finland, M (1950) "Terramycin in pert Clinical and laboratory studies" *Ann N Y Acad Sci*, **53**, 422

Kohn, J L, and Fischer, A E (1947) "Management of whooping cough with special refe to infants" *Amer J dis Child*, **73**, 663.

Lalli, G (1949) "Results obtained by the Italian Air Force in treatment of whooping cough by aeroplane flights" *Rev Med. Aeronaut*, **12**, 237

nicol in treatment of pertussis

" *Brit med J.*, **2**, 1138

ort on 5 severe cases." *Lancet*, **1**, 400

Medical Research Council (1951) "The prevention of whooping cough by vaccination" *Brit. med J*, **1**, 1463

Miller, W J, and Ross, J E (1950) "Aureomycin in the treatment of pertussis a preliminary report" *J Pediat*, **37**, 307

Odegard, A (1946) "Treatment of whooping cough by flying" *Tidsskr norske Laegeforen*, **66**, 574

Rodeman, A C, Bradford, W L, and Berry, G P (1946) "Epidemiological study of outbreak of pertussis in public school" *Amer J Publ Hlth*, **36**, 1156

Wannamaker, L W, Kohn, J L, and Weichsel, M (1949) "Streptomycin in treatment of whooping cough" *Amer J dis Child*, **78**, 201

CHAPTER 8

FUNGOUS INFECTIONS OF THE LUNGS

R. W. RIDDELL

INTRODUCTION

Classification.

The pulmonary mycoses consist of a small number of individual diseases which may be classified as follows.

(1) Infections due to filamentous bacteria-like organisms:
  actinomycosis and nocardiosis.

(2) Infections due to yeast-like fungi:
  (*a*) moniliasis;
  (*b*) torulosis.

(3) Conditions due to *Aspergilli* and similar ubiquitous fungi.
  (*a*) *aspergillosis*,
  (*b*) farmers' lung

(4) Infections due to dimorphic fungi
  (*a*) coccidioidomycosis,
  (*b*) histoplasmosis;
  (*c*) blastomycosis,
  (*d*) sporotrichosis

Laboratory investigations

Although these diseases may be limited to the lungs, the occurrence of disseminated lesions—as for example in bones or skin—may be important in indicating the diagnosis of fungous infection The lungs are the most important site of origin of the systemic mycoses, but the mode of infection in some of them remains obscure. It is thought, however, that infection does not occur from man to man. Once the clinical and radiological findings have suggested the possibility of fungous infection, laboratory investigations are necessary to establish the diagnosis (Conant, *1950*; Riddell, *1951*)

For this purpose, it is important that sputum, bronchoscopic aspirates, and other pathological material should be obtained with minimal exposure to the air, and should be examined as soon as possible, since proliferation of fungi takes place at room temperature This is of particular importance when assessing the significance of potentially pathogenic fungi, as in aspergillosis and moniliasis Direct microscopy of wet preparations is made with 20 per cent sodium hydroxide solution, or by using a stain such as methylene-blue fuchsin Smears should also be fixed, either with Schaudinn's fluid and stained by iron haematoxylin, or by heat and then stained by Gram's method. When there is doubt about the nature of any fungus-like cells present, a fresh wet preparation

of the pathological material should be kept at room temperature in a moist chamber for 2 or 3 days, during which time buds or filaments may be produced from any true fungus cells. Cultures are made at both 22°C. and 37°C on media favourable to fungi but inhibitory to bacteria, such as acid dextrose peptone agar (Sabouraud's medium), or penicillin-streptomycin or tellurite-containing media. Inoculation of experimental animals is often of value, both for the isolation of fungi from pathological material and for the assessment of pathogenicity of a culture isolated Histological sections of biopsy or necropsy material are best stained by the periodic acid Schiff method, and by the use of iron haematoxylin The former differentiates fungi from nuclear material, and is of particular value in facilitating the search for scanty or very small organisms In addition to these general procedures, there are other investigations applicable to particular diseases which will be described under their appropriate sections

Treatment

Any specific measures in treatment will also be mentioned with each disease. It is customary to use potassium iodide in doses of 5 grains thrice daily, increasing slowly until 90 grains or more are being given daily. Any real or apparent clinical improvement achieved during iodide therapy is frequently quoted as conclusive evidence in favour of a fungous aetiology, but such an assumption is unsound

INFECTIONS DUE TO FILAMENTOUS BACTERIA-LIKE ORGANISMS

Actinomycosis and nocardiosis

Causative organisms

Actinomycosis—*Actinomyces israeli*—Anaerobe or micro-aerophile.
Nocardiosis—*Nocardia asteroides*—Aerobe

Actinomyces israeli is a branching filamentous organism of bacterial dimensions, which requires anaerobic or micro-aerophilic conditions for growth. It grows in the form of small white glabrous colonies composed of Gram-positive non-acid-fast filaments, 1 micron in diameter *Nocardia asteroides*, on the other hand, requires aerobic conditions for growth, and forms yellow to orange colonies It very readily fragments into bacillary elements, and is sometimes partially acid-fast, when *Mycobacterium tuberculosis* is simulated in stained preparations

Incidence

These are sporadic diseases which have a world-wide distribution, and most commonly affect young adult males Whereas actinomycosis represents the commonest of the systemic mycotic infections, nocardiosis is rare In actinomycosis, infection occurs endogenously from the normal habitat of the organism in tonsillar crypts and carious teeth (Emmons, 1938 ; Rosebury, 1944 ; Slack, 1942) Primary pulmonary infection probably occurs by aspiration of organisms from such foci, and possibly from tartar material, infection may also be secondary to abdominal actinomycosis *Actinomyces israeli* does not exist as a normal saprophyte outside the human host In contrast, nocardiosis is an exogenous infection, derived from organisms growing saprophytically in soil and dust It is frequently stated that agricultural workers are particularly prone to

actinomycosis, and it has been postulated that this is due to neglected dental hygiene. It is doubtful, however, whether occupation does, in fact, play any part in its aetiology (Davis, 1941), though it certainly does so in nocardiosis, which occurs chiefly in agricultural workers.

Clinical features

Actinomycosis.—It has been estimated that 15 per cent of all cases of actinomycosis are of thoracic origin, whereas 60 per cent begin in the cervico-facial region (Cope, 1938). There are two main forms of pulmonary disease: one is bilateral and consists of multiple small foci of infection, the other is a unilateral disease which may become massive.

The onset of the disease is usually insidious, with slight and irregular fever, cough and expectoration. With the development of suppuration, the sputum, becomes muco-purulent and is sometimes blood-stained. The clinical picture may simulate that of chronic tuberculosis or lung abscess. When infection is extensive, there is often pleural pain, with signs of widespread consolidation, and possibly mediastinal involvement. A chronic empyema, containing foul-smelling pus, may develop (Bowyer, 1949), but more frequently the pleura becomes thickened and adherent. Abscess and sinus-formation often occur in the chest wall in protracted infections. A distinctive feature of the disease is the way in which spread of infection occurs without regard to fascial planes, and over long periods of time. Occasionally, haematogenous metastases occur, for example, in the brain. Radiographs may show irregular shadows of varying size scattered through the lungs, particularly in the mid-zone and basal areas (Fig. 47). Where massive infection with consolidation occurs, extensive homogeneous shadowing is seen, in which small areas of translucency may develop (Fig. 48). Miliary lesions are rare. A loculated empyema may sometimes occur. The most characteristic change is that of periosteal new-bone formation on the under-surface of several contiguous ribs (Fig. 49). These and some vertebrae may become involved,

[illegible]

1944; Meyer and Gall, 1935)

Nocardiosis.—In nocardiosis, the clinical features and course of the disease are similar to those of actinomycosis (Kirby and McNaught, 1946) (Fig. 50), but there is a greater tendency for metastasis to occur to the brain, subcutaneous tissues and other organs. The disease sometimes simulates pulmonary tuberculosis (Glover and his colleagues, 1948).

Laboratory diagnosis

Actinomycosis [illegible] appearance of cream-coloured colonies,
"*sulphur granule* [illegible] -1 *millimetre*
in size, and may [illegible] *ments*, which
represent a tissue reaction. Granules are less often formed in *nocardiosis*. Similar granules may be formed by other fungi or *bacteria and may show peripheral clubs*; it is important, therefore, to demonstrate that such granules consist of branching filaments of about 1 micron in diameter. *Sputum* and cerebro-



FIG 47 — Actinomycosis A 32-year-old male with bilateral disease *Actinomyces israeli* cultured from right empyema fluid Radiograph shows 3–5 millimetre circular shadows scattered throughout both lungs (*By courtesy of Mr O S Tubbs, St Bartholomew's Hospital, London*)



FIG 48 —Actinomycosis A 53-year-old male with unilateral disease and draining sinuses over left upper chest Sulphur granules found in discharge from sinuses Radiograph shows circular shadows in left lung above the homogeneous opacity of the pleural effusion (*By courtesy of Drs R J Reeves and D T Smith, Duke Hospital, N. Carolina*)



Fig 49.—Actinomycosis. A *15-year-old female* with right apical consolidation but no chest-wall induration or sinuses. Cervical vertebrae became involved and death occurred from cerebrospinal meningeal actinomycosis. Radiograph *shows homogeneous* clouding in the right upper zone and periostitis of the upper 7 ribs posteriorly (*By courtesy of Dr. G Simon, Brompton Hospital, London*)



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D. T Smith,
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spinal fluid often contain no granules, but only short lengths of branching filaments (Fig. 51)

Pathological material is spread into thin layers and examined with a lens; it may be necessary to curette the walls of a sinus to obtain suitable material. Smears should be stained with Gram's stain, and by the modified Ziehl-Neelsen method, using 1 per cent sulphuric acid instead of acid-alcohol to identify partially acid-fast organisms Cultures are made on a variety of media, including heart-brain agar and nutrient dextrose agar, and are incubated both anaerobically and aerobically at 37°C. The *Actinomycetes* will not survive the concentration methods used for the isolation of *Mycobacterium tuberculosis*, and are inhibited by media containing antibiotics. Animal pathogenicity tests are not helpful in the diagnosis of actinomycosis, but guinea-pig inoculation is useful in the identification of *Nocardia asteroides*

Sections of biopsy or necropsy tissues are stained by routine methods, with Gram's and modified Ziehl-Neelsen's stains. In actinomycosis the granules consist of filaments which are haematoxyphil and Gram-positive, but the clubs, if present, are eosinophil and Gram-negative Each granule is surrounded by a zone of pus cells, and more peripherally by a chronic inflammatory reaction (Fig 59) In nocardiosis there is, as in actinomycosis, a suppurative pneumonitis, but granule formation is seen less often than in actinomycosis

Serological tests are unhelpful The erythrocyte sedimentation rate is raised and there is usually a neutrophil leucocytosis

Prognosis and treatment

Prognosis is favourable in pulmonary actinomycosis if penicillin is given in adequate dosage The use of sulphadiazine has reversed the almost invariably fatal prognosis in nocardiosis

Penicillin, in doses of at least 1,000,000 units daily, is usually curative in actinomycosis, but is ineffective in nocardiosis If relapse is to be avoided, it is essential that treatment be continued for at least 6–8 weeks after initial improvement is achieved Sulphadiazine, [illegible] in nocardiosis, preferably for 4–6 [illegible] sulphonamides are ineffective in [illegible] be performed on any strain isolated, together with animal protection tests (Boand and Novak, 1949, Runyon, 1951, Strauss, Kligman and Pillsbury, 1951). Potassium iodide may be useful when combined with other medical and surgical measures

At some stage surgical intervention may be required, such as sinus exploration or drainage of an abscess or empyema, and lobectomy or pneumonectomy may be indicated for limited lesions (Wangensteen, 1932)

INFECTIONS BY YEAST-LIKE ORGANISMS

Moniliasis

Causative organism

This is *Candida albicans* The genus *Candida* consists of fungi which predominate in the unicellular form, that is as yeast cells, and which elongate to form filaments in submerged growth Both yeasts and filaments propagate by producing buds (blastospores) close to their extremities (Fig 52). The component species are



FIG 51 —*Actinomyces israeli* in sputum Short branching filaments less than 1 micron in diameter Gram-stained smear (× 850)



FIG 52 — *Candida* species Submerged culture showing characteristics of genus *Candida*. Yeasts and filaments producing blastospores Gram-stained culture (× 400)



FIG 53 —*Cryptococcus neoformans* in exudate The double-contoured wall of the yeast is

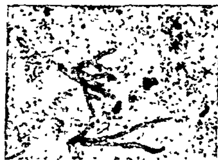


FIG 54 —*Aspergillus fumigatus* in sputum Branching filaments about 4 microns in diameter Stained iron haematoxylin and eosin (× 400)



FIG 55 —*Aspergillus fumigatus* spores in sputum Spore size (*a*) may be compared with neighbouring cocci Wet methylene-blue-fuchsin preparation. (× 400)



FIG 56 —*Coccidioides immitis* Culture grown at 22°C, showing filaments breaking up into deeply-staining chlamydospores Stained with lactophenol cotton blue (× 400)

identified by biochemical reactions, morphology, and pathogenicity tests *Candida albicans* is identified by its fermentation of glucose and maltose with the production of acid and gas, and sometimes of sucrose with acid formation only, and by its failure to ferment lactose Furthermore, under certain conditions of culture, it produces thick-walled spores (chlamydospores) about 8 microns in diameter, and it is lethal when inoculated intravenously in rabbits It is the only *Candida* species which is important as a potential human pathogen

Mode of infection

The fungus is a normal inhabitant of the upper respiratory tract, also of the intestines and skin, infection usually arises endogenously In thrush, superficial mucosal invasion occurs, but occasionally, and particularly in infants of low

determined by bacterial infection, or by some loss of tissue resistance, has not been assessed There is no doubt that fungi may proliferate when the normal bacterial flora is disturbed, as in chronic bronchial infections, or following the use of antibiotics The presence of *C albicans* as a predominant organism, however, does not indicate that it is necessarily playing either a primary or a secondary role as a pathogen, indeed, it is probable that in most instances the fungus

small outbreaks
1944, Ludlam
es, and various

fomites may be responsible for spread of infection

It is doubtful whether or not broncho-pulmonary moniliasis can be looked upon as a sound concept The diagnosis is frequently made on finding *C albicans* in the sputum of a patient in whom areas of patchy clouding or enlarged hilar shadows are seen by radiography, on the absence of tubercle bacilli in the sputum, and on the success of iodide therapy (Baskt, Hazard and Foley, 1934; Brown, 1946, Frank, 1941, Ikeda, 1936, Stovall and Greeley, 1928) Diagnoses based on such data may result in the overlooking of the primary disease It has been suggested that "secondary thrush of the bronchi" is a more appropriate name for the majority of these cases, invasion by the fungus being regarded as secondary (Shrewsbury, 1936) The relationship of radiological shadows to the presence of the fungus in the bronchial tree is still to be determined In infantile infections, peribronchial pneumonia of unidentified aetiology occurs in association with bronchial thrush (Lederer and Todd, 1949), but a pneumonitis due to *Candida albicans* has yet to be demonstrated It is possible that thrush membrane may separate from the bronchial wall and gravitate to cause areas of collapse

Clinical features of moniliasis

The following description of clinical and radiological findings may be taken to represent those most commonly recorded in broncho-pulmonary moniliasis A sub-division is usually made into (1) broncho-moniliasis and (2) pulmonary moniliasis.

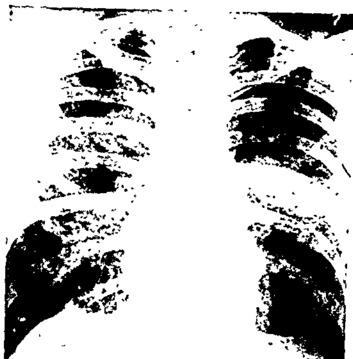


FIG. 57.—Moniliasis A 42-year-old female with a 6 months' history of respiratory infection There was a heavy growth of *Candida albicans* from the sputum She recovered in 3 months with iodide therapy preceded by vaccine desensitization Radiograph shows areas of patchy clouding on the right side with honeycomb shadowing, and massive clouding with an area of translucency in the left mid-zone. (*By courtesy of Drs R. J. Reeves and D T. Smith, Duke Hospital, N. Carolina*)

Broncho-moniliasis—Bronchial disease presents with cough as its most distressing symptom The sputum is scanty and mucoid, and typically it contains small grey flakes in which fungus is present, but it is sometimes described as milky in appearance. The general condition of the patient is unaffected and there is no pyrexia The signs are those of bronchitis Radiography shows faint ill-defined patchy shadows, sometimes with hazy linear streaking extending into the lung fields ; the distribution is chiefly in the mid-zone and basal areas.

Pulmonary moniliasis—Pulmonary moniliasis is less often recorded. Cough is again distressing and the sputum is sometimes blood-stained ; dyspnoea or pain in the chest may be a presenting symptom There is usually some pyrexia, together with increase of pulse and respiratory rates Lesions vary from patchy to widespread consolidation ; pleural effusion has been described Radiographs show ill-defined patchy peripheral shadows, often in two or more lobes, with sparing of the apices in most cases (Fig 57) The shadows are often not static, decreasing in intensity in some areas and increasing in others.

Laboratory diagnosis

[illegible]

of an atypical culture

Sections of histological material are rarely obtained. In thrush, a pseudo-membrane, consisting of fungus, epithelial debris, blood cells and bacteria, develops on the mucosal surface. Fungal filaments infiltrate between the epithelial cells of the oedematous mucosa to reach or perforate the basement membrane. There is submucosal capillary congestion, and, in extensive infections, ulceration occurs The possibility of post-mortem fungous invasion should be considered whenever there is an absence of tissue reaction to the organism in autopsy specimens A skin-testing vaccine is of no value in diagnosis, since positive reactions frequently occur in normal persons Serological tests give irregular results. The blood-leucocyte count and erythrocyte sedimentation rate are described as being normal in broncho-moniliasis, but raised in pulmonary moniliasis

Prognosis and treatment

Both oro-pharyngeal thrush and broncho-pulmonary moniliasis usually respond readily to treatment

The diamidines have been found to be active inhibitors of *C albicans in vitro* (Lacey, personal communication), but their value as effective local therapeutic agents in superficial infections requires further exploration Potassium iodide by mouth has been recommended for the treatment of pulmonary infections, with preliminary desensitization of patients who are hypersensitive to *C albicans* vaccine injected intradermally (Conant and his colleagues, 1948)

Torulosis

Causative organism

The causative fungus in torulosis is *Cryptococcus neoformans.* The genus *Cryptococcus* consists of fungi which occur solely as yeast cells reproducing by forming buds (blastospores) Its component species are identified by morphological, biochemical and pathogenicity tests *Cryptococcus neoformans* produces abundant mucoid capsular material, which in exudates and tissues is sharply demarcated around the organism to form a wide refractile capsule It is the only pathogenic species and is lethal to mice , a non-pathogenic variant also exists

In the early literature, this disease was sometimes known as European blastomycosis, and its causative organism as *Torula histolytica* It has been the subject of a monograph by Cox and Tolhurst (1946)

Mode of infection

The fungus has been isolated from fruit, milk (Carter and Young, 1950), and from the soil (Emmons, 1951) Whilst the mode of infection in torulosis is unknown, the primary focus probably occurs in the lungs, paranasal sinuses or nasopharynx Although there is often evidence of systemic dissemination, ultimate localization of infection is a characteristic feature of the disease. The commonest sites for this to occur are the meninges and central nervous system (Freeman, 1931), producing clinical features resembling tuberculous meningitis ; a history of recent respiratory infection is often obtained in such cases

Pulmonary torulosis, though rarely occurring alone, is common amongst reported cases of the disease It may form a relatively insignificant part of a generalized infection, recognizable only by histological examination, but more



FIG 58.—Torulosis A 12-year-old male with 4 months' history of cough and sputum, night sweats, and loss of weight There was no evidence of lesions elsewhere, and the tumour was successfully removed by upper and middle lobectomy Radiograph shows a well-circumscribed 7-centimetre oval opacity *in the lower third of the right lung* (*By courtesy of Dr B A Dormer, King George V. Hospital, Durban*)

commonly a tumour-like mass (toruloma) is produced. Acute miliary torulosis has been reported

Torulosis may co-exist with tuberculosis (Rappaport and Kaplan, 1926) and with Hodgkin's disease (de Bré and his colleagues, 1947, Fitchett and Weidman, 1934) It has been suggested that the number of cases in which torulosis and Hodgkin's disease have been coexistent is greater than can be accounted for by mere chance, and that the latter may predispose to mycotic infection.

Incidence

Torulosis is a sporadic disease of world-wide occurrence, is most common in adults, and is slightly more frequent in males than females

Clinical features of torulosis

This disease is accompanied by relatively little constitutional disturbance, and there may be no pyrexia or only low-grade fever (Hamilton and Tyler, 1946) Cough with scanty mucoid [illegible]
in the chest is sometimes pr [illegible]
sive infection develops, of [illegible]
of unresolved or atypical pneumonia Alternatively, the disease presents as an expanding intrathoracic tumour (Dormer and Scher, 1947) Rarely, a pleural effusion is formed, and the yeast has been demonstrated in an empyema (Reeves, Butt and Hammack, 1941) Bronchial obstruction has only once been reported (Moody, 1947)

Areas of clouding which tend to become confluent are seen by radiography, especially involving mid-zone or basal areas A toruloma is seen as a dense, homogeneous, well-defined shadow, simulating a new growth or lung abscess Fig 58) In some cases the clear outline of the tumour itself is obscured by the



FIG. 59 —Pulmonary ...



FIG 60 —*Candida albicans* in sputum Yeast cells and filaments present in thrush membrane Wet methylene-blue-fuchsin preparation (×400)



FIG. 61 —Pulmonary torulosis Wall of

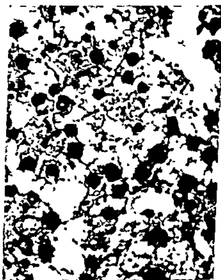


FIG 62 —Pulmonary torulosis. Section

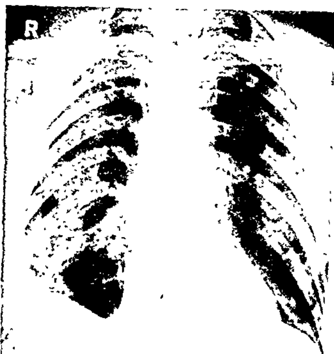


FIG. 63 —Aspergillosis A 55-year-old male, who developed post-operative pulmonary infarcts from thromboses of leg veins. *Histology of autopsy material showed* fungus colonies associated with an area of infarction Radiograph taken 1 week after operation shows 5–8 millimetre well-defined shadows in the right mid-zone (*By courtesy of Dr. G. Simon, Brompton Hospital, London*)

process simulating either tuberculosis (Donaldson, Koerth and McCorkle, 1942; Schneider, 1930), or a neoplasm (Yesner *and Hurwitz,* 1950)

In the cases described, the disease usually has an insidious onset, sometimes with a lengthy history of recurrent pulmonary or pleural infections Evidence of earlier pulmonary infarction may be obtained Haemoptysis may for a long time be *the only symptom There may be dyspnoea and cough with mucoid or* muco-purulent sputum, often becoming blood-stained In extensive disease there are remittent fever, night sweats, and deterioration in weight and general health

Irregular clouding or small circumscribed shadows in the bases or mid-zones are sometimes seen in radiographs (Fig 63) Another finding is a dense tumour-like opacity, which slowly develops central translucency, and in which a movable shadow may persist (Shanks and Kerley, 1951).

Laboratory diagnosis

The possibility of a secondary *Aspergillus* infection of an inflammatory or neoplastic process must be considered. The repeated finding of filaments of about 4 microns in diameter is important suggestive evidence of primary or secondary aspergillosis (Fig 54), *but cultural confirmation is necessary since similar appearances may be given by other* "contaminants". On the other hand, thick-walled spores, about 3 microns in diameter, are of less *significance, since these often result from recent inhalation* (Fig 55) *Aspergillus fumigatus* grows rapidly on Sabouraud's dextrose agar at 37°C Colonies are at first white and

filamentous, but quickly become covered with dull-green spores (Thom and Raper, 1945).

In primary lesions, fungous colonies are found, both within alveoli and invading their walls, and are associated with areas of tissue necrosis (Fig 65). These may be immediately surrounded by neutrophil leucocytes, and more peripherally by chronic inflammatory cells. Local vessels are frequently thrombosed and invaded by fungus filaments. Occasionally the organism is found in areas of broncho-pneumonia (Cooper, 1946). In secondary infections, there are varying degrees of invasion of cavity walls. It is only when fungal filaments reach the lumen of a cavity or bronchus that sporing heads of *Aspergillus* are formed (Fig 66). Dermal and serological tests are unhelpful.

Prognosis and treatment

Bronchial disease and limited infections are benign, unless the cause of severe haemoptyses. Massive infections with abscess formation may be fatal. Oral iodide therapy appears to be effective. Desensitization has been recommended when the patient is shown to be hypersensitive to the causative fungus. Extirpation of a tumour-like lesion may be indicated (Yesner and Hurwitz, 1950), as for example, when it is causing recurrent haemoptyses.

Farmers' lung

Causative organisms

Possibly these are spores of various ubiquitous fungi.

Mode of infection

This term is used for an occupational disease occurring among hay and grain workers, and among stable-men and cattle-men (Campbell, 1932; Fawcitt, 1938). A similar condition exists among workers handling mouldy materials in the manufacture of textiles. Unlike aspergillosis, fungous invasion of pulmonary tissue does not occur, and it has been suggested that the symptoms result from a state of hypersensitivity or irritation due to inhalation of large quantities of spores, rather than to plant dust as in the byssinosis of cotton-mill workers. Cases are often seen in groups, especially during threshing time and when hay, collected in wet seasons, is being handled. Spores of *Aspergillus*, *Penicillium* and *Mucor*, and of other ubiquitous fungi, have been implicated (Fawcitt, 1938), but they commonly occur in sputum of persons working in dusty atmospheres.

Clinical features

These conditions require further study, but the following description is intended to summarize the more important findings. The disease may closely simulate the ordinary forms of asthma, chronic bronchitis, or even broncho-pneumonia, but its occupational and seasonal incidence, its sudden onset, and the exacerbations of extreme dyspnoea without a corresponding degree of bronchial spasm, all make it a clinical entity of its own. The dyspnoea increases in severity until it becomes so acute that patients are unable to climb even the slightest inclines. Any further contact with the excitant dust leads to a bout of coughing, during which only scanty, colourless, mucoid and frothy sputum is expectorated. There may be mild pyrexia. The signs described are those of bronchitis or of patchy



FIG. 64—Farmers' lung. A 39-year-old male farm-worker with 2 years' *history* of gradually increasing dyspnoea associated with inhalations of hay dust. There was little cough and no fever, but health deteriorated Species of *Aspergillus*, *Penicillium* and *Mucor* were cultured from his sputum, which was scanty Radiograph shows patchy peripheral clouding with honeycomb shadowing *mainly on the right* side (*By courtesy of Dr. R Fawcitt, West Highland Hospital, Oban*)

ulmonary consolidation Later, when dyspnoea becomes extreme, there may be yanosis and emaciation.

Radiology—At first there is a fine honeycomb shadowing, most marked in the iddle and lower zones, and elsewhere the normal pulmonary markings become iore clearly defined because of emphysema. In recurrent cases, these earlier ppearances *proceed to patchy clouding, later becoming dense and coalescent,* id there may be enlargement of hilar shadows, the sharp definition of silicotic dules is not seen (Fig 64) X-ray appearances have led to a misdiagnosis of berculosis

iboratory diagnosis

Investigations are undertaken as described under "Aspergillosis" Note is ade of any fungi cultured and of any which predominate. The isolation of contaminants" growing at 37°C, even if lethal on animal inoculation, is not

e stained, to exclude

ic acid Schiff method

thological findings have only once been recorded, they consisted in emphysemous and *ruptured alveoli, acute congestion of vessels, and much* patchy rosis (Fawcitt, 1936) Skin-tests and serological examinations are unhelpful. cording to a personal communication by C J Fuller, there may be slight cocytosis but eosinophilia is uncommon, sputum examination rarely shows an ess of eosinophils



FIG 65 —Pulmonary aspergillosis Colonies of *Aspergillus fumigatus* in lung Section stained with iron haematoxylin and eosin (×400)



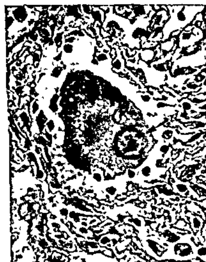


FIG 67 — Pulmonary coccidioidomycosis Giant cell containing a thick-walled immature sporangium of *Coccidioides immitis* (*d*), which has not yet formed endospores Section stained with haematoxylin and eosin (×400)

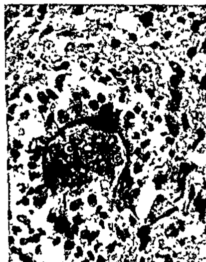


FIG 68 — Pulmonary coccidioidomycosis Rupture of mature sporangium of *Coccidioides immitis*, liberating endospores (*e*) Section stained with haematoxylin and eosin. (×400)

Prognosis and treatment

This is not a fatal condition, and, although there is great incapacity while in contact with the excitant dust, there is usually rapid improvement when the patient is removed from this environment. Administration of potassium iodide by the mouth is beneficial. Antihistamine drugs have given no improvement in the few cases in which they have been used by C. J. Fuller (personal communication).

INFECTIONS DUE TO DIMORPHIC FUNGI

Coccidioidomycosis

Causative organism

The fungus responsible is *Coccidioides immitis*.

In saprophytic life in the soil (Emmons, 1942), and in cultures at 22°C. and 37°C., this fungus exists only as a white filamentous growth, which segments into chains of resistant spores (chlamydospores), 2×5 microns in size. In animal tissues, however, these spores enlarge, become spherical, and finally form thick-walled non-budding cells (sporangia), 20–80 microns in diameter, which are filled with large numbers of endospores, 2–5 microns in diameter (Figs. 67 and 68).

Mode of infection

Infection normally occurs by inhalation of chlamydospores in dust, and small explosive outbreaks may occur in groups of people who become exposed. Dust-control measures have been effective in reducing the incidence of infection. The disease, which has been reviewed by Forbus and Besterbreutje (1946) and by Perry (1950), closely simulates tuberculosis in having a primary respiratory infection (Dickson and Gifford, 1938), which is benign and usually asymptomatic, and a secondary, frequently fatal, progressive form. It is almost entirely confined to the arid south-western regions of the United States of America, where it is endemic, though a few cases have occurred in South America and in Italy. Elsewhere, the disease is seen only as a laboratory infection acquired from cultures of the fungus, which are highly infectious (Nabarro, 1948; Smith and Harrell, 1948). The primary disease affects males and females about equally, but males progress to the disseminated granulomatous disease twice as often as do females. Coloured races are particularly prone to the development of progressive infections. The disease may occur at any age, but whereas primary infections are most common in infants and children, systemic disease is met with chiefly in adults. Coccidioidomycosis may coexist with tuberculosis (Firestone and Benson, 1949; Hyde and Hyde, 1949).

The two forms of the disease are considered separately.

Primary coccidioidomycosis

Clinical picture.—More than 60 per cent of all infections are subclinical. Fever, pain in the chest, and cough occur in symptomatic cases after an incubation period of 1–3 weeks. The symptoms may be those of a mild cold, or else of a more severe respiratory infection with expectoration and rigors, and sometimes arthralgia. Haemoptysis is rare, and is usually associated with the presence of a

cavity Allergic manifestations, in the form of erythema nodosum and erythema multiforme, often appear within 8–14 days after the onset of symptoms Physical signs may or may not be present, and are those of bronchitis and patchy consolidation of the lungs, occasionally with a pleural effusion A cavity may develop and must be differentiated from those due to other causes (Winn, 1941)

Diagnosis —Radiological signs are usually seen even in asymptomatic infections (Colburn, 1944, Jamison and Carter, 1947) Irregular areas of clouding, sometimes extensive and often associated with enlarged hilar shadows, are common early changes (Fig 69), hilar lymphadenopathy alone is less common The lung fields usually clear in 1–2 months, but may leave residual well-defined areas of shadowing (Fig 70) or, rarely, opacities consistent with calcification (Bass, Schomer and Berke, 1948, Jamison, 1946) Occasionally they give rise to a thin-walled cavity, usually in the upper zone (Smith, Beard and Saito, 1948) (Fig 71) Pleural effusion is uncommon

Progressive coccidioidomycosis

Clinical picture —This develops as a continuation of the more severe cases of primary disease, although it may be delayed as much as 6 months The primary lesions fail to resolve and new foci appear in several parts of the lungs, often, too, in bones and skin, a terminal meningitis develops in about 25 per cent of these cases There are continuous low-grade fever, anorexia and loss of weight, muco-purulent sputum and, later, cyanosis occur The physical signs are those of broncho-pneumonia Cold abscesses, sometimes forming extensive sacculate deposits of pus, develop more frequently than in tuberculosis Acute dissemination sometimes takes place, and the clinical features then simulate those of miliary tuberculosis

Radiography —Radiological signs are an extension of those seen in primary disease, they are often surprisingly widespread, and usually resemble those of tuberculous broncho-pneumonia (Fig 72) Miliary shadows are less sharply demarcated in outline than in tuberculosis Vertebrae, ribs, and bones of the hands and feet, may show small sharply circumscribed areas of translucency, with a predilection for bony prominences (Benninghoven and Miller, 1942, Miller and Birsner, 1949), and with little surrounding bone reaction

Laboratory diagnosis

Sporangia are only occasionally found by direct examination of sputum or bronchial aspirates in the primary disease, but are more constantly present in progressive infections Gastric contents, pus or pleural fluid should also be examined Demonstration of the fungus in these materials is more successful by culture After about 1 week, flat filamentous colonies appear, and within about 2–3 weeks these have become white and fluffy, and consist of filaments and chlamydospores (Fig 56) Great care should be taken in handling these cultures, slopes rather than plates should be used for all except very young growths Mice are inoculated intraperitoneally with pathological material or cultures, sporangia are produced after a few days, and later there is a terminal dissemination

In tissue sections various stages in the development of sporangia are found (Figs 67 and 68) When endospores are liberated from mature sporangia they

FIG 69. — Primary coccidioidomycosis A 32-year-old female laboratory worker whose symptoms followed use of a culture of *Coccidioides immitis.* Malaise, right-sided chest pain, dry cough, and erythema nodosum were present. *Coccidioides immitis* was isolated from sputum by animal inoculation Rapid improvement and complete recovery Radiograph shows scattered small circular shadows in periphery of right mid-zone, and isolated 1 cm shadows in left upper and middle zones. (*By courtesy of Drs. A Morland and J D N. Nabarro, University College Hospital, London*)

FIG 70 — Primary coccidioidomycosis Primary disease in which partial resolution has occurred, leaving persistent granuloma Radiograph shows well-defined shadows, circular to oval, 0 5–1 cm, in the right middle and lower zones (*By courtesy of Dr J W Birsner, Bakersfield, California*)

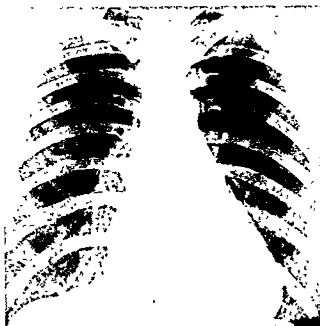


FIG 71. — Primary coccidioidomycosis Primary disease in which resolution has occurred, leaving only a solitary cavity Radiograph shows a thin-walled cavity with a fluid level in the right midzone (*By courtesy of Dr J. W Birsner, Bakersfield, California*)



FIG 72 — Disseminated coccidioidomycosis. The limited primary infection has progressed to disseminated disease Radiograph shows 1-3 mm, densely distributed, circular shadows throughout both lungs (*By courtesy of Dr J W. Birsner, Bakersfield, California*)

incite a local neutrophil leucocyte response They enlarge to form new sporang either locally or after lymphatic or blood-stream dissemination, and these larg cells incite a chronic inflammatory reaction, often with giant cells Pneumonit occurs in primary infection, and, when this fails to resolve, healing is usuall by fibrosis. A cavity probably results from the ballooning of a small caseo necrotic area in relation to a partially occluded bronchus In progressive disease there is a caseating broncho-pneumonia, and lesions are almost identical with those produced by *Mycobacterium tuberculosis*

Antigen in diagnosis—A skin-testing antigen, coccidioidin, is prepared as for tuberculin and is used similarly (Smith and his colleagues, 1948) The test is very specific when critical dilutions are used (Smith and his colleagues, 1949) and is valuable both in clinical diagnosis and in epidemiological studies It becomes positive about 10 days after infection, though this reaction may be delayed by about a month The reaction continues to be positive except in some severe progressive cases, and becomes increasingly positive during clinical improvement High dilutions of antigen should be used for the skin-testing of patients with erythema nodosum Since the coccidioidin reaction becomes positive before antibodies are present in the serum, the skin test is a useful diagnostic procedure Coccidioidin is used as antigen in serological tests Antibodies are rarely detectable in mild primary infections, though they are usually found when symptoms are severe; a diagnostic titre for precipitins is much more frequent than for complement-fixing antibodies In progressive disease, antibodies are almost invariably present, the precipitin titre tends to fall, and complement-fixing antibody titre to rise, with severity of the disease (Smith and his colleagues, 1950)

Blood tests—The erythrocyte sedimentation rate is elevated in primary disease, returning to normal with resolution, but remains raised if dissemination occurs There is an initial leucocytosis in the first week of infection; anaemia develops in progressive disease

Prognosis

Complete recovery is usual in primary disease, even when severe, and the coccidioidin sensitivity which remains is associated with lasting immunity The occurrence of allergic skin lesions, or of a pulmonary cavity, is coincident with high immunity A residual granuloma may persist without harmful effect for months or years Progressive disease is frequently fatal, though it occasionally undergoes spontaneous arrest, and the outlook is most favourable in cases in which hypersensitivity to coccidioidin is maintained

Treatment—Rest is advised in primary disease until the symptoms have abated and the erythrocyte sedimentation rate is normal, there is no specific treatment Surgical excision of a residual primary lesion has been recorded (Greer, Forsee and Mahon, 1949; Moore and his colleagues, 1949), but such intervention is necessary only if pneumothorax fails to control repeated haemoptyses, or if a tension cyst develops. Symptomatic care is indicated in systemic infections, cold abscesses require aspiration, and isolated subcutaneous or osseous granulomas should be excised whenever this is practicable

Histoplasmosis

Causative organism

Histoplasma capsulatum is the causative fungus in histoplasmosis.

In saprophytic life in the soil (Emmons, 1949) and in culture at 22°C, th fungus exists in a white mould-like form, in which thick-walled, spherical spore (chlamydospores), 7–15 microns in diameter, are formed, and are characterized by their tuberculate surfaces (Fig. 76). On the other hand, in infected tissues and in culture on enriched media at 37°C, the fungus grows in the form of small yeasts, 2–4 microns in diameter.

Mode of infection

The disease has been reviewed by Parsons and Zarafonetis (1945), by Riddell (1951), and by Hodgson, Weed and Clagett (1950). Its mode of infection is unknown, but probably occurs by ingestion or inhalation of the mould-like form of the fungus. Most people are refractory to infection, which may take one of two forms. The first is produced by reticulo-endothelial invasion and, whilst the clinical manifestations are protean, the most common findings are irregular low-grade fever, hepatomegaly, splenomegaly, anaemia and leucopenia. The other form of the disease, the existence of which is as yet controversial, is a benign pulmonary infection, which is usually asymptomatic and may simulate tuberculosis radiologically. Whereas the disseminated disease is world-wide and sporadic, it would appear that the benign pulmonary form is more limited geographically.

Benign pulmonary infection.—The existence of a benign form of histoplasmosis, analogous to primary coccidioidomycosis, is postulated from the frequent association between pulmonary calcification and hypersensitivity to histoplasmin in east-central and south-central areas of the United States of America (Christie, 1950; Furcolow, Mantz and Lewis, 1947; High, Zwerling and Furcolow, 1947). Calcification of this type was found in tuberculin-negative residents of Tennessee (Gass and his colleagues, 1938), and it was later demonstrated elsewhere that in similar cases tuberculin sensitivity developed after B.C.G. (Bacille Calmette-Guérin) vaccination (Aronson, Saylor and Parr, 1942). Then came the discovery that a high proportion of these patients were positive reactors to histoplasmin (Christie and Peterson, 1945; Palmer, 1945), and many individuals, originally non-reactors to histoplasmin, were observed to develop pulmonary lesions with simultaneous conversion of the histoplasmin reaction to positive (Furcolow, 1949; Furcolow, Mantz and Lewis, 1947). Although the evidence in favour of this hypothesis is largely circumstantial, *Histoplasma capsulatum* has been cultured from tubercle-like granulomas, and from sputum and gastric washings in these cases (Christie, 1950; Furcolow, 1950). It is possible, however, that the development of increasing sensitivity to histoplasmin, which occurs with age in "endemic" areas, may be due to fungi only immunologically related to *H. capsulatum*.

It is doubtful whether there has been a single instance of infection contracted in Great Britain, and negative results have so far been obtained from the limited histoplasmin skin-testing surveys performed (McCracken, 1948; McWeeney and

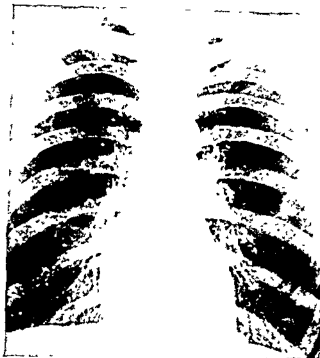


FIG 73—Benign histoplasmosis. A 43-year-old male with a history of dry cough for 9 years, but without abnormal signs or symptoms Histoplasmin skin test, 1 : 100, positive History of 3 years' residence in Canada with visits to the U S A Radiograph shows 2–3 mm well-defined circular shadows of high density scattered throughout both lung fields. *Not shown on reproduction but visible on original,* were faint opacities around some of these shadows (halo shadows) *(By courtesy of Prof J Crofton, Edinburgh University)*

his colleagues, 1946) A close association has been shown to exist in Great Britain between pulmonary calcification in children and tuberculin sensitivity (Thompson, 1948) Three possible cases of healed pulmonary histoplasmosis, in British patients who had resided in Canada and the United States, have been recorded (Arblaster, 1950 ; Crofton, 1950) (*see* Fig 73)

Incidence of histoplasmosis

The infection occurs more commonly in males than in females, and, although it may present at any age, about 16 per cent of recorded cases have occurred in infants of less than 1 year of age Combined infection with tuberculosis has been reported (Meleney, 1941)

Clinical features of histoplasmosis

Pulmonary disease occurs in about 50 per cent of all cases of generalized histoplasmosis, but infection is only very rarely limited to the respiratory tract. The symptoms are non-specific and are overshadowed by those of reticulo-endothelial disease They include cough, expectoration, dyspnoea, and pain in the chest, hoarseness and haemoptysis are less frequent Pyrexia is usually present Oro-pharyngeal and laryngeal mucosal ulcerations have been reported (Weed and Parkhill, 1948) Benign pulmonary histoplasmosis is practically asymptomatic.

Radiological signs

In benign histoplasmosis there is most frequently a single well-defined shadow,

FIG 74—Histoplasmosis. (a) A case of early pulmonary histoplasmosis with minimal general dissemination (April 1947). Radiograph shows 3 mm. low-density circular shadows here and there on both sides. (b) The same case in January 1949. Radiograph shows central calcification with peripheral halos in many of the lesions. (By courtesy of Dr J. C. Peterson, Vanderbilt University, Nashville, Tennessee.)

(a)

(b)

½–3½ centimetres in diameter, situated in any part of the lungs. This is often associated with enlarged hilar lymph nodes in which calcification sometimes develops Less often, such shadows are larger with poorly defined margins, and more than one may be present. In occasional patients who are usually with symptoms, and in those with disseminated histoplasmosis, there are persistent patchy shadows scattered throughout both lungs Calcification frequently occurs in the centres of lung lesions, but may take 2 or more years to become visible radiographically (Furcolow, 1949, Sontag and Allen, 1947) (Fig 74*a* and *b*) When the scattered shadows are of small size miliary tuberculosis is simulated, but the halo shadows around central calcifications, and the regularity of dense circular shadows which may later remain, are characteristic of histoplasmosis (Figs. 69 and 74*b*) Cavitation does not occur, and hilar lymphadenopathy is only rarely present alone.

Laboratory diagnosis

Smears of sputum or bronchial aspirates are best stained by Giemsa's method The causative organism occurs as *very small encapsulated yeast cells, usually* intracellular in monocytes, or sometimes in neutrophil leucocytes The capsule of this yeast is a very narrow one. In cultures, a white fluffy growth develops in about 2 weeks at 22°C, and later develops typical chlamydospores (Fig 76); cultures should be retained for at least 4 weeks before a negative report is given Gastric contents, sternal marrow, and blood should similarly be examined Pathological material and cultures are inoculated intraperitoneally into mice; reticulo-endothelial invasion occurs as in human disease.

Biopsy.—Diagnosis has been established by biopsy examination in about 33 ... Lung lesions may be minute, ... entral necrosis, and contain

Antigen in diagnosis.—The skin-testing antigen, histoplasmin, prepared as for tuberculin and coccidioidin, is still an experimental one The test is performed in the same manner as the tuberculin test, using a critical dilution of the antigen, and a positive reaction is considered to denote past or present infection It may be of value in epidemiological surveys of the benign form of the disease, but it is of only limited clinical value since negative skin tests occur in 50 per cent of ... antibodies are often

Prognosis and treatment

Benign pulmonary histoplasmosis is usually asymptomatic Disseminated infections are frequently fatal in infants and in children, but complete recovery is possible (Bunnell and Furcolow, 1948). Disease in adults may be prolonged for months or years, and may not be fatal Absence of antibodies early in the disease appears to indicate a poor prognosis There is no specific treatment.

Blastomycosis

Causative organisms

These are of two kinds: (1) *Blastomyces dermatitidis* (causing North American

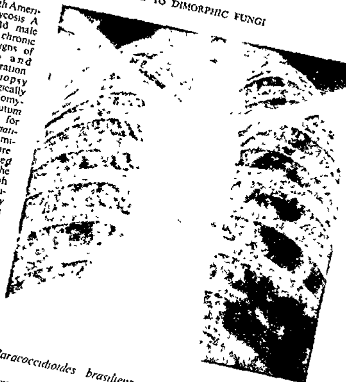


FIG. 75.—North American blastomycosis. A 43-year-old male farmer with chronic cough and signs of pulmonary and laryngeal infiltration. Laryngeal biopsy was cytologically positive for blastomycosis and the sputum was positive for *Blastomyces dermatitidis* by direct examination and culture. Necropsy showed blastomycosis of the lungs. Radiograph shows multiple irregular areas of patchy clouding on both sides, together with some streaky shadowing. Heart and trachea markedly displaced to the right. (*By courtesy of Drs. R. J. Reeves and D. T. Smith, Duke Hospital, N. Carolina.*)

blastomycosis), (2) *Paracoccidioides brasiliensis* (causing South American blastomycosis).

At 22°C these fungi form white mould-like growths, whilst in human tissues and when cultured on enriched media at 37°C, they adopt a yeast-like phase. This consists of thick-walled yeast cells, 8–15 microns in diameter, forming single buds (blastospores) at one pole in the case of *Blastomyces dermatitidis* (Fig. 78), and much larger cells, up to 60 microns in diameter, which may produce multiple blastospores in that of *Paracoccidioides brasiliensis* (Fig. 79).

Mode of infection

Infection in these diseases is probably of pulmonary origin and from an exogenous source, although the causative fungi have not been demonstrated in nature.

North American blastomycosis

Incidence.—This disease has been reviewed by Martin and Smith (1939), Starrs and Klotz (1948) and by Schwarz and Baum (1951). It appears to be confined to the central and south-eastern parts of the United States of America. Infection may take one or other of two forms, namely: (1) systemic disease, and (2) cutaneous disease (chiefly involving exposed parts). Adult males are the most common sufferers. Only 1 case has been reported in Great Britain (Dowling and Elworthy, 1925).

Clinical features.—In pulmonary disease the symptoms are those of a subacute respiratory infection. There is low-grade fever, dyspnoea, cough, and sometimes pain in the chest; the sputum is often blood-stained. Later there is increasing dyspnoea, and loss of weight and strength Pleural involvement and sinus formation occur, but less frequently than in actinomycosis

Radiologically, widespread ill-defined patchy shadows are often seen (Fig 75). Massive opacities may appear in advanced disease, and may contain small irregular areas of translucency. Mediastinal lymphadenopathy is very frequently present. Miliary shadows occasionally occur (Solway, Kehan and Pritzker, 1939). Any bones may be involved, particularly the vertebrae and ribs when the appearances resemble tuberculosis, such lesions tend to be more extensive than in actinomycosis.

South American blastomycosis

Incidence.—This disease occurs only in South America; it has been described by Almeida and his colleagues (1942), and by Lacaz (1951) Young adult males are most commonly affected.

Clinical features.—Visceral infections are much less frequent than the involvement of cutaneous, muco-cutaneous and lymphatic tissues. In 20 per cent of systemic infections, however, the lungs are affected. Pulmonary disease simulates North American blastomycosis, but massive lesions are unusual and lymphadenopathy is more frequent

Laboratory diagnosis of blastomycosis

Yeast cells are searched for in exudates In cultures at 22°C. white fluffy colonies develop after about 10 days Mice are inoculated intraperitoneally with ground-up saline suspensions of pathological material or cultures Histo- [illegible] yeast cells amongst collections of neutro- [illegible] age of cell contents [illegible] e of encapsulation.

A skin-testing vaccine gives positive reactions in cutaneous infections in North American blastomycosis, but negative results occur in 50 per cent of the systemic infections. Complement-fixing antibodies may be present in the serum. Systemic disease is usually fatal It is doubtful whether it is possible to assess prognosis from the results of skin tests and serum-antibody estimations

Treatment

[illegible] has [illegible] American blastomycosis, but sulphonamides have given [illegible] improvement in a number of cases

Sporotrichosis

Causative organism

The organism which causes sporotrichosis is *Sporotrichum schenckl*

This fungus exists in saprophytic life—for example, on plants and timber—and in culture at 22°C., as a white to grey-black mould-like growth In this



FIG 76 [illegible]

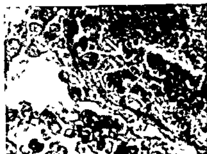


FIG 77 [illegible]

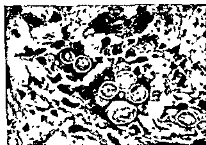


FIG 78 —Pulmonary blastomycosis (North-American) Thick-walled yeast cells of *Blastomyces dermatitidis*, forming single buds Section stained with haematoxylin and eosin (×750)

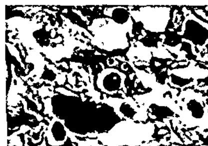


FIG 79 —Pulmonary blastomycosis (South-American) Thick-walled yeast cells of *Paracoccidioides brasiliensis*, forming multiple buds Section stained with haematoxylin and eosin (×750)



FIG 80 —*Sporotrichum schenckl* Culture grown at 22°C showing fine filaments, bearing spores in terminal digitate arrangement and along their sides Stained with lactophenol cotton blue (×400)



FIG 81 —*Sporotrichum schenckl* in exudate. Fusiform yeast cells (*g*), present in purulent exudate resulting from animal inoculation Gram-stained (×400)

phase the organism consists of delicate filaments, 2 microns in diameter, which bear club-shaped spores, 3×5 microns in size, found in terminal digitate groups or in lines along their sides (Fig 80). In animal tissues, and in culture on enriched media at 37°C, it takes the form of fusiform budding yeast cells, mostly about 2–4 microns in size

Cutaneous infection occurs as the result of traumatic inoculation of the organism into the skin, usually by infected plants or wood. Systemic spread is rare (Collins, 1947), and, in contrast with other systemic mycoses, the lungs are practically never involved The disease has been reviewed by Norden (1951) It is world-wide and usually sporadic, but has assumed epidemic proportions in South African mines (Transvaal Chamber of Mines, 1947), and it may be endemic in the north-central areas of the United States of America (Foerster, 1926) and in France

Laboratory diagnosis

The criteria for diagnosis of most reported cases of pulmonary disease have been inadequate Direct examination of sputum and of bronchial aspirates is unlikely to show the causative yeasts, since the fungus can rarely be seen in human material, though it may be cultured (Smith, 1945) *Sporotrichum schencki* appears within 5–20 days' incubation at 22°C as small, bacterium-like colonies, grey-white in colour, which enlarge and become membranous, glistening and starfish-shaped Pathological material or cultures are injected intratesticularly into rats, or intraperitoneally into mice, an acute inflammatory reaction results, in which large numbers of fusiform yeasts are present (Fig 81).

A skin-testing vaccine has been used, and positive reactions appear to demonstrate past or present infection Precipitin estimation appears to be the most sensitive serological test

Prognosis and treatment

Sporotrichosis responds more dramatically to iodide therapy than does any other fungous disease Surgery is contra-indicated

BIBLIOGRAPHY

Introduction

Conant, N F (1950) "Laboratory Diagnosis of Pulmonary Mycoses." *Amer Rev Tuberc*, *61*, *690*

Riddell, R W (1951) "Laboratory Diagnosis of Common Fungus Infections." In *Recent Advances in Clinical Pathology*, 2nd ed, chapter 5, p 77. London; Churchill

Actinomycosis and nocardiosis

Benbow, E P., Smith, D T., and Grimson, K S. (1944). "Sulfonamide Therapy in Actinomycosis" *Amer Rev. Tuberc*, *49*, *395*

Boand, A, and Novak, M (1949) "Sensitivity Changes of *Actinomyces bovis* to Penicillin and Streptomycin" *J Bact.*, *57*, *501*

Bowyer, H. W. (1949) " ... Empyema." *Brit med J*, 2, 848

Cope, V Z (1938). ... Press

Davis, M I J (1941 ... with Special Reference to its

... *omyces bovis* from Tonsillar Granules" *Publ*

... d Pfuetze, K. H. (1948). "*Nocardia asteroides* ..." *J Amer med. Ass.*, *136*, *172*.

Kirby, W M M, and McNaught, J. B (1946) "Actinomycosis due to *Nocardia asteroides*" *Arch intern. Med*, 78, 578
Lubert, M (1944) "Actinomycosis of the Vertebrae" *Amer. J. Roentgenol*, 51, 669.
Meyer, M, and Gall, M B (1935) "Mycosis of the Vertebral Column" *J Bone Jt Surg*, 17, 857
Rosebury, T (1944) "The Parasitic Actinomycetes and other Filamentous Micro-organisms of the Mouth" *Bact Rev*, 8, 189.
Runyon, E H (1951). "*Nocardia asteroides* Studies of its Pathogenicity and Drug Sensitivities" *J Lab. clin Med*, 37, 713.
S [illegible] " *J Bact*, 43, 193
S [illegible] "Chemotherapy of Actinomycosis [illegible]
Wangensteen [illegible] Actinomycosis of the Thorax with Report of a Case Successfully Operated upon" *J thorac Surg*, 1, 612

Moniliasis

Anderson, N A, Sage, D N, and Spaulding, E H (1944) "Oral Moniliasis in Newborn Infants" *Amer J Dis Child*, 67, 450.
Baskt, H J Hazard, J B, and Foley, J A (1934) "Pulmonary Moniliasis" *J Amer. med Ass*, 102, 1209
Brown, T. G (1946) "Pulmonary Mycosis" *Edinb. med J* 53, 583.
Conant, N F, Martin D S, Smith D T, Baker, R D and Callaway, J L (1944) "Moniliasis" In *Manual of Clinical Mycology* Philadelphia, Saunders
Frank, T J F (1941) "Bronchopulmonary Moniliasis." *Rov. Melb Hosp clin. Rep.*, 12, 11
Ikeda, K (1936) "Bronchopulmonary Moniliasis its Relation to Obscure Chronic Infection" *Arch. Path, Chicago* 22, 62
Lederer, H, and Todd, R M (1949) "Thrush in Infancy" *Arch Dis Childh*, 24, 200
Ludlam, G. M, and Henderson, J L (1942) "Neonatal Thrush in a Maternity Hospital" *Lancet*, 1, 64
Shrewsbury, J. F D (1936) "Secondary Thrush of the Bronchi" *Quart J Med*, 5, 375
Smith, L W, and Sano, M. E (1933) "Moniliasis with Meningeal Involvement" *J infect Dis*, 53, 187
Stovall, W D, and Greeley, H P (1928) "Bronchomycosis" *J Amer. med Ass*, 91, 1346
Wessler, S, and Browne, H R (1945). "*Candida albicans* Infection with Blood Stream Invasion" *Ann intern Med*, 22, 886

Torulosis

Carter, H S, and Young, J L (1950) "Note on the Isolation of *Cryptococcus neoformans* from a Sample of Milk" *J Path Bact*, 62, 271.
Collins, V P (1950) "Bone Involvement in Cryptococcosis" *Amer J Roentgenol* 63, 102
Cox, L B, and Tolhurst, J C (1946) *Human Torulosis* Melbourne, University Press
Crone, J T, de Groat, A F, and Wahlin, J G (1937) "Torula Infection" *Amer J Path* 13, 863.
de Bré, R., Lamy, M, Leblois, C, Nick, J, Grumbach, Mlle, and Normand, E (1947) "Sur [illegible]
Dorr [illegible]
Dorr [illegible]
Eme [illegible]
Fitch [illegible]
Free [illegible] 43, 236.
Greening, R R, and Menville, L. J (1947) "Roentgen Findings in Torulosis" *Radiology*, 48, 381
Hamilton, J B, and Tyler, G R (1946) "Pulmonary Torulosis" *Radiology*, 47, 149.

o

Hardaway, R. M, and Crawford, P M (1935) "Pulmonary Torulosis." *Ann intern Med*, **9**, 334
Hirsch, E. F., and Coleman, G H. (1929). "Acute Miliary Torulosis of the Lungs." *J. Amer. med Ass*, **92**, 437.
Moody, A. M. (1947). "Asphyxial Death due to Pulmonary Cryptococcosis *Calif. Med*, **67**, 105.
Rappaport, B Z, and Kaplan, B (1926) "Generalized *Torula* mycosis" *Arch Path, Chicago*, **1**, 720
Reeves, D L, Butt, E M, and Hammack, R W (1941) "*Torula* Infection of the Lungs and Central Nervous System." *Arch intern Med*, **68**, 57.
Sheppe, W M. (1924) "*Torula* Infection in Man" *Amer J. med. Sci*, **167**, 91.
Stone, W J, and Sturdivant, B F (1929) "Meningo Encephalitis due to *Torula histolytica*" *Arch intern Med*, **44**, 560
Wiener, M F (1951) "Generalized Torulosis with Bone Involvement." *Arch. intern Med*, **87**, 713
Wilson, H M, and Duryea, A W (1951) "Cryptococcus Meningitis (Torulosis) Treated with a New Antibiotic Actidione" *Arch Neurol Psychiat*, **66**, 478.

Aspergillosis

Cawley, E P (1947) "Aspergillosis and the *Aspergilli*" *Arch. intern Med*, **80**, 423.
Cooper, N S (1946) "Acute Bronchopneumonia due to *Aspergillus fumigatus Fresenius*" *Arch Path, Chicago*, **42**, 644
Delikat, E (1945) "Acute Pulmonary Mycosis" *Lancet*, **2**, 370.
Donaldson, J M., Koerth, C J, and McCorkle, R G (1942). "Pulmonary Aspergillosis" *J. Lab clin Med*, **27**, 740
Gersil, B., Weidman, W. H, and Newman, A V. (1948) "Pulmonary Aspergillosis with Report of 2 Cases" *Ann intern Med*, **28**, 662.
Henrici, A T (1939) "An Endotoxin from *Aspergillus fumigatus*." *J Immunol*, **36**, 319
Heppleston, A G, and Gloyne, S R. (1949) "Pulmonary Aspergillosis in Coal Workers." *Thorax, Lond*, **4**, 168
Schneider, L V (1930) "Primary Aspergillosis of the Lungs." *Amer. Rev. Tuberc*, **22**, 267.
Shanks, S C, and Kerley, P (1951) *A Textbook of X-ray Diagnosis*, Vol 2, p 442. London, Lewis
Thom, C., and Raper, K B (1945). *A Manual of the Aspergilli*. Baltimore, Williams & Wilkins
Van Ordstrand, and Scott, H (1940) "Pulmonary Aspergillosis with Report of a Case" *Cleveland clin. Quart*, **7**, 66
Yesner, R, and Hurwitz, A. (1950) "A Report of a Case of Localized Bronchopulmonary Aspergillosis Successfully Treated by Surgery." *J. thorac. Surg*, **20**, 310

Farmers' lung

Campbell, J. M. (1932) "Acute Symptoms Following Work with Hay." *Brit. med J*, **2**, 1143
Fawcitt, R. (1936). *Brit J Radiol*, **9**, 186
— (1938) "Occupational Diseases of the Lungs in Agricultural Workers." *Brit J. Radiol*, **11**, 378.

Coccidioidomycosis

Bass, H E., Schomer, A, and Berke, R (1948). "Coccidioidomycosis. Persistence of Residual Pulmonary Lesions" *Arch. intern Med*, **82**, 519
Benninghoven, C D., and Miller, E. R. (1942). "Coccidioidal Infection in Bone." *Radiology*, **38**, 663.
✓ Colburn, J. R. (1944). "Roentgenological Type of Pulmonary Lesions in Primary Coccidioidomycosis." *Amer. J. Roentgenol*, **51**, 1.
Dickson, E. C, and Gifford, M. A (1938) "*Coccidioides* Infection. the Primary Type of Infection." *Arch intern Med*, **62**, 853.
Emmons, C W (1942). "Isolation of *Coccidioides* from the Soil and Rodents." *Publ Hlth Rep, Wash*, **57**, 109
✓ Firestone, G. M., and Benson, E S (1949) "Co-existing Disseminated Coccidioidomycosis and Tuberculosis" *Amer. Rev Tuberc.*, **59**, 415

Forbus, W. D , and Besterbreutje, A M (1946) Coccidioidomycosis a Study of 95 Cases of the Disseminated Type with Special Reference to the Pathogenesis of the Disease " *Milit Surg* , **99**, 653

Greer, S J , Forsee, J H , and Mahon, H W. (1949) " Surgical Management of Pulmonary Coccidioidomycosis in Focalized Lesions " *J thorac Surg* , **18**, 591

Hyde, B , and Hyde, L (1949) " Disseminated Coccidioidomycosis and Lymphohaematogenous Tuberculosis " *Arch intern Med* , **83**, 505

Jamison, H W (1946) " A Roentgen Study of Chronic Pulmonary Coccidioidomycosis " *Amer J Roentgenol* , **55**, 396

— and Carter, R A (1947). " The Roentgen Findings in Early Coccidioidomycosis " *Radiology*, **48**, 323

Miller, D , and Birsner, J W (1949) " Coccidioidal Granuloma of Bone " *Amer J. Roentgenol* , **62**, 229

Moore, J A , Murphy, J D , Oteen, N C , and Ward, D E (1949) " Coccidioidomycosis Report of Surgical Excision of Residual Primary Granulomata and Cavities " *J thorac. Surg* , **18**, 484

✓Nabarro, J D N (1948) " Primary Pulmonary Coccidioidomycosis Case of Laboratory Infection in England " *Lancet*, **1**, 982

Perry, C B (1950) " Coccidioidomycosis " In *British Encyclopaedia of Medical Practice*, 2nd ed , Vol 3, p. 520 London , Butterworth

Smith, C E , Beard, R R , and Saito, M T (1948) " Pathogenesis of Coccidioidomycosis with Special Reference to Pulmonary Cavitation " *Ann intern Med* , **29**, 623

— Saito, M T , Beard, R R , Kepp, R M , Clarke, R W., and Eddie, B U (1950) " Serological Tests in the Diagnosis and Prognosis of Coccidioidomycosis " *Amer J Hyg* , **52**, 1

— [illegible]

— [illegible]

Smit [illegible]

Win [illegible]

Histoplasmosis

Arblaster, P G (1950) " Pulmonary Histoplasmosis " *Thorax, Lond* , **5**, 333

Aronson, J D , Saylor, R M , and Parr, E L (1942) " Relationship of Coccidioidomycosis [illegible] *Chicago*, **34**, 31

[illegible] on 10 Proved Cases of Histoplasmosis "

[illegible] Calcification." *Ann N Y Acad Sci* , **50**, 1283

— and Peterson J C (1945) " Pulmonary Calcification in Negative Reactors to Tuberculin " *Amer. J publ Hlth* , **35**, 1131

✓Crofton, J. (1950) " A Probable Case of Pulmonary Histoplasmosis Diagnosed in England " *Thorax, Lond* , **5**, 340

Emmons, C. W (1949) " Isolation of *Histoplasma capsulatum* from Soil " *Publ Hlth Rep* , *Wash* , **64**, 892

Furcolow, M L (1949) " Development of Calcification in Pulmonary Lesions associated with [illegible]

— [illegible]

— [illegible]

62, 1711

Gass, R S , Gauld, R. L., Harrison, E. F., Stewart, H. C , and Williams, W. C. (1938). " Tuberculosis Studies in Tennessee " *Amer Rev Tuberc* , **38**, 441.

CHAPTER 9

LUNG ABSCESS

W. P Cleland

DEFINITION

A LUNG abscess, strictly speaking, should refer to a collection of pus in the lung tissues and must therefore be distinguished from other collections occurring in pre-existing cavities or potential spaces Encysted and interlobar empyemas, infected cysts and bronchial and bronchiectatic abscesses are examples of the latter group, each of which may be incorrectly regarded as a lung abscess

The term, lung abscess, was, however, originally employed to describe any pulmonary cavity containing pus, later it was used to cover a wide variety of suppurative lesions in the lung of varying aetiology and pathology This inevitably led to a great deal of confusion Recently it has become apparent that the development of an abscess represents but one aspect, albeit a very important one, of a pulmonary infection in which suppuration and necrosis of varying degrees dominate the picture

It is proper, therefore, that any study of this problem should include all such conditions and not be restricted merely to those in which an abscess proper has formed

CLASSIFICATION

In spite of careful research and intensive thought in the past, no completely satisfactory classification has yet been evolved Many aspects of the condition have [illegible]

groups ([1] putrid or anaerobic and [2] non-putrid or aerobic) this distinction being based on the presence or absence of a foul odour of the sputum They regarded these two as distinct entities with differing pathology, course and prognosis, and requiring radically different management Barrett (1944) regards the solitary putrid lung [illegible]

account of staphylococcal and Friedlander abscesses, which he regards as separate entities with a distinct aetiology, course and treatment Although he considers anaerobic and aerobic groups separately, he regards this sub-division as one of convenience providing a primary sub-division which facilitates further study Nicholson (1950) postulates that both the aerobic and anaerobic abscesses are caused by the aspiration or inhalation of infected material into the bronchial tree, and thus have a common aetiology He points out that " aspiration pneumonia " varies considerably in severity, forming a series ranging from cases in which

High, R H, Zwerling, H B, and Furcolow, M L (1947) "Disseminated Pulmonary Calcification" *Publ Hlth Rep, Wash*, 62, 20
Hodgson, C H, Weed, L A, and Clagett, O T (1950) "Pulmonary Histoplasmosis: Review of Published Cases and Report of an Unusual Case." *J thorac. Surg*, 20, 97.
McCracken, B H (1948) "Intrapulmonary Calcification and Histoplasmin sensitivity" *Thorax, Lond*, 3, 45
McWeeney, E. J, Crowe, M, Dunlevy M, and Magan, M. (1946). "A Survey with Histoplasmin in Dublin" *J med Ass Eire*, 19, 162
Meleney, H E (1941) "Pulmonary Histoplasmosis Report of 2 Cases" *Amer. Rev Tuberc*, 44, 240
Palmer, C E (1945) "Nontuberculous Pulmonary Calcification and Sensitivity to Histoplasmin" *Publ Hlth Rep, Wash*, 60, 513
Parsons, R J, and Zarafonetis, C. J D (1945) "Histoplasmosis in Man" *Arch. intern. Med*, 75, 1
Riddell, R W (1951) "Histoplasmosis." In *British Encyclopaedia of Medical Practice*, 2nd ed, Vol 6, p 560 London, Butterworth
Saslaw, S, and Campbell, C C (1950) "Serologic Studies in Histoplasmosis." *Amer. J. publ Hlth*, 40, 427
Sontag L W, and Allen, J E (1947) "Lung Calcifications and Histoplasmin-tuberculin Skin Sensitivity" *J Pediat*, 30, 657
Thompson, B C (1948) "Calcified Foci within the Thorax of English Children." *Thorax, Lond*, 3, 43
Weed, L A, and Parkhill, E M (1948) "The Diagnosis of Histoplasmosis in Ulcerative Disease of the Mouth and Pharynx" *Amer J. clin. Path*, 18, 130

Blastomycosis

Almeida, F de, Lacaz, C da Silva, and Neto, C F (1942) "Dados estatisticos sôbre o granuloma *Paracoccidioidico* no Brasil Importancia de seu estudo." *An Fac. med, S. Paulo*, 18, 137
✓ Dowling, G B, and Elworthy, R, R (1925) "Case of Blastomycotic Dermatitis (Gilchrist)" *Proc R Soc Med*, Vol 19, Sect Dermatol, p 4
Lacaz, C, da Silva (1951) "Lesoes pulmonares na blastomicose sul-americana *O Hospital, Rio de Janeiro*, 39, 405.
Martin, D S, and Smith, D T (1939). "Blastomycosis" *Amer. Rev. Tuberc.*, 39, 275 and 488
Scharz, J, and Baum, G L (1951) "Blastomycosis" *Amer J. clin. Path*, 21, 999.
Springfield (Ill.). Thomas.
Case of Disseminated Blastomycosis"
in Blastomycosis." *Arch intern Med*,
[illegible]

Sporotrichosis

Collins, W. T (1947) "Disseminated Ulcerating Sporotrichosis with Widespread Visceral Involvement" *Arch. Derm Syph, Chicago*, 56, 523
Foerster, R H (1926). "Sporotrichosis an Occupational Dermatosis." *J. Amer med Ass* 87, 1605
Norden, A. (1951) "Sporotrichosis" *Acta path microbiol. scand* Suppl No 89.
Smith, D. T. (1945). "Pulmonary Mycoses Sporotrichosis" *Clinics*, 4, 1021.
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The term, lung abscess, was, however, originally employed to describe any pulmonary cavity containing pus; later it was used to cover a wide variety of suppurative lesions in the lung of varying aetiology and pathology. This inevitably led to a great deal of confusion. Recently it has become apparent that the development of an abscess represents but one aspect, albeit a very important one, of a pulmonary infection in which suppuration and necrosis of varying degrees dominate the picture.

It is proper, therefore, that any study of this problem should include all such conditions and not be restricted merely to those in which an abscess proper has formed.

CLASSIFICATION

In spite of careful research and intensive thought in the past, no completely satisfactory classification has yet been evolved. Many aspects of the condition have been carefully studied: the quality and bacteriology of the sputum, the anatomical distribution, the clinical course and the radiological features, amongst others, have been used, alone or in combination, by various authors as a basis for classification. Neuhof and Touroff (1936, 1940, 1941, 1942) suggested that there were two main groups ([1] putrid or anaerobic and [2] non-putrid or aerobic) this distinction being based on the presence or absence of a foul odour of the sputum. They regarded these two as distinct entities with differing pathology, course and prognosis, and requiring radically different management. Barrett (1944) regards the solitary putrid lung

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Hodgson, C H, Weed, L A, and Clagett, O T (1950) "Pulmonary Histoplasmosis. Review of Published Cases and Report of an Unusual Case." *J. thorac Surg.*, 20, 97
McCracken, B H (1948) "Intrapulmonary Calcification and Histoplasmin sensitivity." *Thorax, Lond*, 3, 45
McWeeney, E J, Crowe, M, Dunlevy M, and Magan, M (1946). "A Survey with Histoplasmin in Dublin" *J med Ass Eire*, 19, 162.
Meleney, H E (1941) "Pulmonary Histoplasmosis Report of 2 Cases" *Amer Rev Tuberc*, 44, 240
Palmer, C E (1945) "Nontuberculous Pulmonary Calcification and Sensitivity to Histoplasmin" *Publ Hlth, Rep, Wash*, 60, 513
Parsons, R J, and Zarafonetis, C J D (1945) "Histoplasmosis in Man." *Arch intern Med*, 75, 1
Riddell, R W (1951) "Histoplasmosis" In *British Encyclopaedia of Medical Practice*, 2nd ed., Vol 6, p 560 London; Butterworth
Saslaw, S., and Campbell, C C. (1950). "Serologic Studies in Histoplasmosis." *Amer. J. publ Hlth*, 40, 427.
Sontag, L W, and Allen, J E (1947) "Lung Calcifications and Histoplasmin-tuberculin Skin Sensitivity" *J Pediat*, 30, 657.
Thompson B C (1948) "Calcified Foci within the Thorax of English Children" *Thorax, Lond*, 3, 43
Weed, L A, and Parkhill, E M (1948) "The Diagnosis of Histoplasmosis in Ulcerative Disease of the Mouth and Pharynx" *Amer J. clin Path*, 18, 130

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Martin, D S, and Smith, D T (1939) "Blastomycosis" *Amer. Rev. Tuberc*, 39, 275 and 488
Scharz, J., and Baum, G L (1951). "Blastomycosis" *Amer J. clin Path*, 21, 999
Smith, D T (1947) *Fungus Diseases of the Lungs*, p 12 Springfield (Ill.); Thomas
Solway, L. J, Kehan, M, and Pritzker, H G (1939) "A Case of Disseminated Blastomycosis" *Canad med Ass J*, 41, 331
Starrs R A, and Klotz, M O. (1948) "North American Blastomycosis." *Arch intern Med*, 82, 1 and 29

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Foerster, R. H (1926) "Sporotrichosis an Occupational Dermatosis." *J. Amer. med Ass* 87, 1605
Norden, A. (1951) "Sporotrichosis" *Acta path microbiol scand* Suppl No 89.
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an abscess Infected pyaemic emboli, however, are in a different category ; they frequently give rise to abscesses in the lung, which are usually small, multiple, and scattered widely throughout the lungs.

Bronchial embolism

A clinical study of the anatomical distribution of lung abscesses suggests that the site of the initial lesion is determined by gravity or posture The majority occur in the posterior segment of the upper lobe or the apex of the lower lobe ; these areas lie in a dependent position when the patient is supine, as, for example, whilst asleep, under anaesthesia or in coma During World War II several cases of middle-lobe and lingular abscesses were encountered in patients who had been immersed in the sea These individuals would usually be in a prone or semi-prone position whilst attempting to swim, and it seems probable that in this position inhaled material would gravitate to the anterior aspect of the lungs Brock and his colleagues (1942), using small intratracheal injections of iodized oil, demonstrated that gravity determines the distribution of the " embolus ", and that in the supine position the posterior segment of the upper lobe and apex of the lower lobe are outlined with oil When the patient is lying on his side the axillary aspect of the lung receives the oil

The nature of the inhaled material is of some importance in determining the sequence of events Inhalation of bacteria, for instance, results in a pneumonic process, whereas the inhalation of infected fluid material, such as vomit or water, produces a diffuse broncho-pneumonia often with suppuration Particulate infected material, however, results in abscess formation In this latter group, it appears that bronchial occlusion leads to a segmental atelectasis, which is then invaded by the organisms carried down with the embolus to form an abscess

Bacterial invasion

Pneumococcal or streptococcal pneumonia is rarely complicated by abscess formation Occasionally, during resolution, translucent areas are visible radiologically, but it is probable that these are areas of resolving and aerating lung tissue rather than cavities containing pus Such an interpretation is supported by the absence of clinical evidence of abscess formation Staphylococcal pneumonia, on the other hand, is not infrequently complicated by true abscess formation The abscesses present several unusual features they are frequently multiple and greatly distended with air , they are often empty ; their size and number may bear no relation to the clinical state of the patient Response to chemotherapy is usually good and complete resolution occurs In these cases the pulmonary lesions are associated with a generalized staphylococcal infection which may dominate the clinical picture

[illegible]

Natural defences against embolism

If bronchial embolism is the important aetiological factor in the production of a lung abscess, it is relevant to consider the natural defences of the body against

rative changes are slight (benign aspiration pneumonia) to those in v
suppuration and necrosis are dominant (acute solitary abscess). More
ints out that the odour of the sputum depends on the organisms prese
utum and the presence or absence of anaerobic conditions of growth,
not imply a specific lesion.

; important to emphasize that no case of lung abscess is strictly primary
rm, " idiopathic lung abscess ", should never be used, for, as Brock rem
e engenders complacency and stultifies attempts to improve our knowl
condition Acceptance of the proposition that lung abscesses are al
dary should encourage the clinician to seek and remove the causative fa
ler to prevent a repetition of the disease.

classification adopted here is, therefore, a practical one, based essent
aetiological factors, because these are by far the most important from
of view of the patients' future welfare and the prevention of subseq
ion It should also have the effect of encouraging clinicians to seek
of the abscess and not be satisfied with a bald diagnosis of " lung absce

CLASSIFICATION

A *Due to specific pneumonias*
- (1) Pneumococcal
- (2) Streptococcal
- (3) Staphylococcal
- (4) Actinomycotic
- (5) Friedländer's
- (6) Amoebic

B *Due to bronchial occlusion*
- (1) Carcinoma
- (2) Benign tumours of the bronchus
- (3) Broncho-stenosis
- (4) Intrabronchial foreign bodies
- (5) Atelectatic

C. *Due to vascular embolism*
- (1) Infarct
- (2) Pyaemic

D *Traumatic*
- (1) Infected haematoma of lung
- (2) Foreign body in lung

E *Non-specific suppurative pneumonia*—aspiration pneumonia

PATHOGENESIS

necessary, whereas Allen (1928) concludes that bronchial embolism is
tant factor. *Clinical research has, however,* gone a long way to solving
m and there is now little doubt that bronchial embolism is the most import
in the majority of cases. Briefly the evidence is as follows.



FIG 82—Lobectomy specimen of a chronic thick-walled abscess containing a slough of lung tissue



FIG 83—Tomograph of large abscess in left upper lobe showing the sponge-like appearance of an enormous slough The slough represented the greater part of the apical and posterior segments of the upper lobe

ich an event and the factors which may lead to a decrease of their vigilance
Negus (1937) considers that the following all play a protective role.

Closure of the larynx —This usually prevents the inhalation of larger particles, whilst its extreme sensitivity and the forceful coughing which follows stimulation should result in the expulsion of smaller particles Its protective role, however, is eliminated during anaesthesia and coma

Cough —This is provoked by stimulation of the larynx, the trachea and the larger bronchi The bronchioles, and probably the smaller bronchi, are relatively insensitive so that stimulation by irritating material will not produce coughing. There are, however, certain aspects of the cough mechanism which are not wholly advantageous to the expulsion of foreign material The initial inspiration whict precedes a cough is accompanied by widening of the bronchi, which may permit a foreign body to descend farther into the depths of the bronchial tree. During the expiratory " squeeze " the bronchi contract , a smooth or semi-solid foreign body will be expelled towards the trachea during this phase, but an irregular or jagged one may be firmly grasped by the contracting bronchus and prevented from moving The blast of air which follows the opening of the larynx dislodges foreign matter and carries it towards the trachea In patients with airless lung distal to a blocked bronchus, this mechanism cannot operate, so that expulsion of the bronchial contents is not achieved This phenomenon can be seen during bronchoscopy performed for post-operative atelectasis The affected bronchus is filled with pus or mucus, which remains motionless even during violent coughing. The cough reflex is depressed by morphine and its derivatives, by anaesthesia, and during sleep or coma

Cilia —The mucosa of the trachea and bronchi are lined by ciliated columnar epithelium, which in turn is covered in health by a thin layer of mucus Ciliary action makes this mucous sleeve flow slowly upwards towards the trachea and larynx, rather in the manner of an escalator The mucous carpet not only entangles foreign particles in its mesh but is also bacteriostatic The ciliary mechanism is undoubtedly of very great importance and is largely responsible for conveying debris from insensitive to sensitive areas of the bronchial tree. Ciliary action is depressed by many factors, such as dehydration, alterations in pH, drugs, and anaesthetic vapours

Sleep —The protective mechanisms described above are all reduced during sleep particularly when the latter is unduly heavy, such as may follow a period of extreme exhaustion or alcoholic indulgence , they are almost entirely eliminated during anaesthesia and in coma

The upper respiratory tract —The upper respiratory tract provides a constant source of material which, under suitable condition, may lodge in the bronchial tree and remain there Mucus and muco-pus from infected tonsils and nasal sinuses, particles of dental tartar, pus or debris from pyorrhoea or dental caries, and blood clot following trauma or surgery to the upper respiratory tract, all may readily reach the bronchial tree when the defences are broken down. These emboli are not only able to occlude a small segmental bronchus, producing atelectasis, bu many of them contain potentially pathogenic organisms, which under suitabl conditions may invade the atelectatic portion of lung and produce a suppurativ pneumonia

FIG 82 —Lobectomy specimen of a chronic thick-walled abscess containing a slough of lung tissue

PATHOLOGY

anges in the lung

cclusion of a bronchus, resulting from embolism, gives rise to an area of neumonitis and atelectasis in the lung beyond the block. This may be patchy, egmental or lobar in distribution The atelectatic area is invaded by organisms arried down with the embolus, producing a suppurative pneumonia.

Suppurative pneumonia

The subsequent changes in this area of suppurative pneumonia depend on (1) the nature of the invading organisms, (2) the resistance of the host, and (3) the presence or absence of ischaemic changes in the involved area It is probable that vascular thrombosis occurs in many of these cases, resulting in necrosis and death of portion of the lung. In this way, quite large areas of lung can be destroyed and the element of necrosis added to that of suppuration The necrotic area may be quite small (Fig 82) or so large as to constitute an entire segment or lobe (Fig 83) A slough, so formed, slowly separates from the surrounding tissues and comes to lie free within the abscess cavity Small sloughs may soon disintegrate and the fragments be expectorated Larger sloughs may remain intact for prolonged periods, acting as foreign bodies within the abscess cavity, where their presence prevents resolution and healing

It is thus obvious that the two distinct elements of suppuration and necrosis are operating in varying degrees in cases of pulmonary suppuration At one end of the scale, suppuration is predominant, giving rise to a suppurative pneumonia, aerobic abscess or spreading suppurative pneumonitis At the other end, necrosis is an important additional factor, giving rise in its most severe form to acute pulmonary gangrene, whereas less extensive changes result in the acute putrid, anaerobic or solitary lung abscess The odour of the pus in these cases is due to the invasion of the necrotic lung tissue by anaerobic organisms

It is emphasized above that the lung lesions in this condition are basically segmental in distribution (*see* Fig 84) This implies that the involved area has a wide base presenting on the parietal or interlobar aspect of a lobe with the narrower apex of the triangle in the hilar region As a result the pleural surfaces are affected by the inflammatory process at an early stage, resulting in the formation of localized adherence between the two layers of pleura The importance of this event will be apparent when surgical drainage is considered. It would seem surprising that, in the presence of a fulminating infection, perforation into the pleura does not occur at an early stage with the production of an empyema. Barrett (1944) however, has drawn attention to the ischaemic changes occurring elsewhere in the segment, and which escape the ischaemic changes and presence of a sub-pleural plexus of blood vessels, which serve to nourish and maintain a thin fringe of lung tissue at the periphery of the abscess

Rupture

Accumulation of pus produces distension of the abscess cavity (Fig 84*c*) until finally it ruptures into the bronchial tree Evacuation of the contents results in the production of considerable quantities of purulent sputum and permits air to

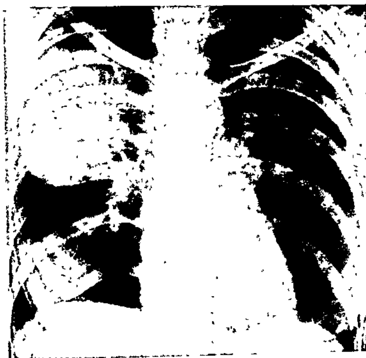


(a)

FIG 84—Putrid abscess in the posterior segment of right upper lobe (a) and (b) show segmental consolidation

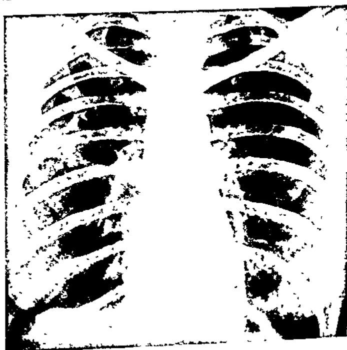


(b)



(c)

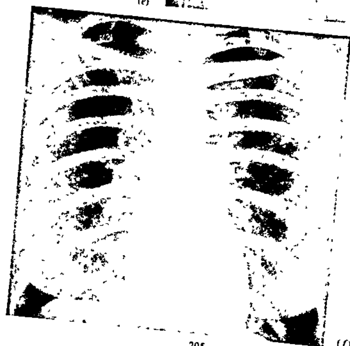
FIG 84 (*cont*) —(*c*) Cavity distended with pus, (*d*) showing considerable resolution after physiotherapy, (*e*) tomogram showing small residual cavity, (*f*) demonstrating eventual resolution



(*d*)



(e)



(f)

enter the cavity from the bronchial tree Thus, for the first time, the x-ray films will show an abscess cavity containing air and, perhaps, a fluid level.

Rupture of the abscess into the bronchial tree *commonly* takes place during the second week of the disease, but may be considerably delayed ; if the bronchial opening is large enough and the contents of the abscess are sufficiently liquid, evacuation will be complete *and healing will commence.*

Resolution

Resolution is, however, a relatively slow and gradual process and, owing to the degree and intensity of the surrounding pneumonitis, it often takes several weeks before cavitation is no longer visible radiologically.

Delayed resolution and chronicity are usually due to the persistence of sloughs in the abscess cavity (Fig 82), to inadequate bronchial drainage, or to persistent infection in the surrounding lung tissue The residual changes in the lung, or sequelae, depend upon the volume of destroyed lung and also upon the rapidity with which infection can be controlled Of these two factors the latter is probably the more important, for it is not uncommon to obtain complete restitution to normal following a large abscess which has been treated early and adequately (*see* Fig 85) Conversely, permanent bronchiectatic or cystic changes are commonly found when *an abscess has been present for longer than 3–4 months* Bronchography is necessary to evaluate these late changes, which vary from a normal bronchial tree to some dilatation and irregularity of involved bronchi (Fig 86), or even a small residual cavity or cystic space (Fig 87).

Healing

Healing of an abscess, from the pathological point of view, may assume one of several forms In the most complete form the breach in the lung is obliterated by compensatory expansion of surrounding normal lung tissue and by some degree of fusion by fibrosis *Complete healing such as this can probably only occur in* [illegible] treated In the more persistent [illegible] the mouths of the [illegible] ory in type, but it [illegible] An epithelialized cavity may represent bacteriological healing but does constitute an anatomical abnormality, which cannot disappear spontaneously and may act as *locus minoris resistentiae* at a later date

Involvement of the bronchi

The bronchi adjacent to the diseased area have inevitably taken part in the [illegible] damage This may either be slight and [illegible] tation

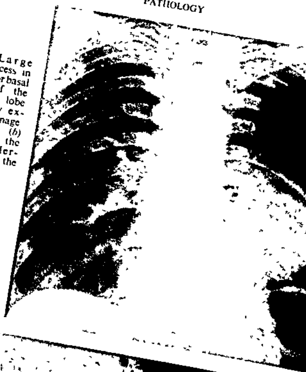
Spread of disease

Other areas of the lung

Involvement of new areas of lung occur by one or other of two mechanisms.

(1) Direct invasion of adjacent lung tissue is common, particularly in the early stages before rupture has occurred This may well account for the frequency

FIG 85 — Large putrid abscess in the posterior basal segment of the left lower lobe treated by external drainage (a) and (b) demonstrate the very considerable size of the abscess



(a)

L

(b)

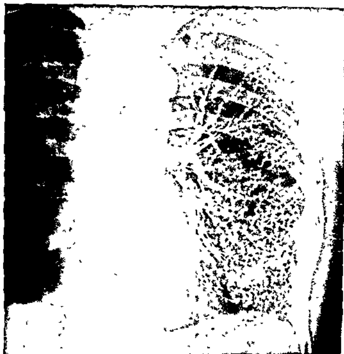


Fig. 85 (*cont*) —(*c*) and (*d*) Bronchograms taken after healing showing a practically normal bronchial tree

(*c*)



(*d*)

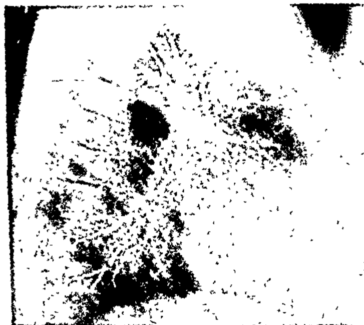


FIG 86 —Right lateral bronchogram to show residual bronchiectasis of the posterior branch of the right upper lobe bronchus following an abscess treated by external drainage

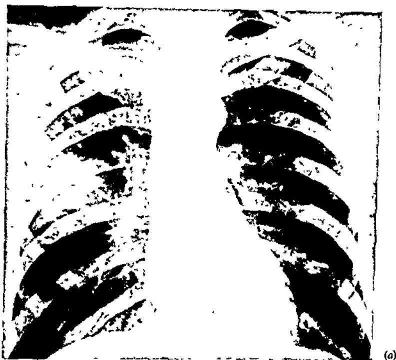
with which multiple loculi are encountered Extension across a major fissure into an adjacent lobe is by no means uncommon (Fig 89)

(2) Spread to more distant portions of lung occurs by "bronchial embolism", infected particles from the abscess, travelling *via* the bronchial tree, are arrested in a bronchus where a second or "spill-over" abscess is initiated (Fig 87*b*) Bronchial embolism is particularly apt to occur when normal coughing is depressed, as in sleep or anaesthesia, or after surgical drainage when the presence of an external bronchial fistula disturbs the normal expulsive efforts Emboli may lodge in any part of either lung

The pleura

Localized fibrinous inflammation always occurs in the pleura overlying the abscess The fibrinous deposits soon organize, and adherence between the visceral and parietal layers of the pleura results These adhesions appear early and are of considerable practical importance, their presence acts as a barrier to the direct invasion of the pleural cavity, and through this localized adherent area it is possible to carry out surgical drainage without transgressing a free and vulnerable pleural cavity

Effusions and empyema, however, are quite common in spite of the development of protective adhesions, they may occur spontaneously or follow ill-advised

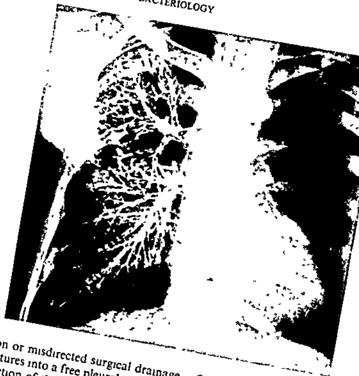


(a)



(b)

Fig 87 — Putrid abscess in upper lobe treated by two-stage drainage (a) Shows original abscess in axillary aspect of upper lobe, (b) after first-stage drainage showing metal marker and a spill-over abscess above the original lesion, (c) bronchogram showing two types of residual bronchial damage At the site of the original abscess *the bronchi* are crowded, distorted and slightly dilated; *the spill-over abscess* has left a small cystic cavity



(c)

attempts at aspiration or misdirected surgical drainage Occasionally an abscess, at an early stage, ruptures into a free pleural cavity, producing gross contamination and fulminating infection of the very large serous surface This is an uncommon event in adults, but it occurs frequently in staphylococcal abscesses in children

The brain

Cerebral abscesses were a frequent complication of pulmonary suppurative lesions before the advent of antibiotics Routine use of these agents has greatly reduced the incidence of this serious complication Infected emboli may reach the brain through a systemic artery or by retrograde flow through the prevertebral plexus of veins which extends from the chest to the skull Experimental injection of opaque media demonstrates the ease with which emboli can follow this latter route The lesions are usually multiple, but autopsy records of solitary abscesses are sufficiently common to justify surgical attempts at removal if only one absce is suspected

BACTERIOLOGY

Specific infection

The role played by *Staphylococcus aureus*, Friedlander's bacillus and the fungus causing actinomycosis in the production of a lung abscess is mentioned above These organisms can undoubtedly be solely responsible for abscess formation, but proof of their responsibility rests with the isolation of the organisms from the sputum in pure or nearly pure culture in the early stages After bronchial drainage



Fig. 88 — Specimen of chronic lung abscess showing smooth glistening epithelialized lining of the cavity



Fig 89 —Specimen of left lung showing multiple abscess cavities and pulmonary suppuration The spread of the disease has been partly due to direct extension and partly by bronchial embolism

has been established for some time, the primary organisms are usually overshadowed by the growth of secondary invaders, whilst conversely both the staphylococcal and the Friedlander organisms may act as secondary invaders of existing lesions

Non-specific infection

The bacteriology of the non-specific abscess is much more obscure For many years spirochaetes and fusiform bacilli and anaerobic streptococci have been isolated from lung abscesses, these being similar in all respects to organisms normally found in the upper respiratory tract They have been regarded as primarily responsible by some authors but merely as accidental secondary invaders by others Experimentally, however, mixed cultures of these organisms, or material scraped from infected teeth, will produce a lung abscess when injected into the trachea of animals (Smith, 1927 and 1932) They flourish in anaerobic conditions and produce marked foetor of the pus With bronchial drainage well established, aerobic conditions replace anaerobic ones in the abscess so that these organisms will fail to thrive and foetor will disappear Should anaerobic conditions reappear, however, these organisms may once more thrive and foetor consequently return Available evidence thus suggests that these organisms are responsible for the formation of an abscess in some cases

In many cases even the careful anaerobic culture of sputum fails to reveal specific organisms, and one can only assume that a variety of organisms, both aerobic and anaerobic, can be responsible for the bacterial invasion which follows bronchial embolism It does seem probable, however, that the presence of anaerobes results in a more virulent type of infection and is more commonly associated with significant necrosis of lung tissue

CLINICAL FEATURES

Onset

The onset is usually sudden and influenzal in type, with fever, malaise, headache and generalized aches and pains Within a relatively short period the patient may become toxic and gravely ill In less severe and atypical cases, the onset is more insidious and may occasionally be so mild that the patient is not even confined to bed The early administration of antibiotics has resulted in a marked increase of this more vague and insidious type Post-operative cases deserve special emphasis, for the symptoms are often masked by the after-effects of anaesthesia and surgery In such cases fever, malaise, a slight cough with sputum, and pain in the chest may be present , too often these manifestations are negligently put down to post-operative bronchitis without giving due consideration to more serious conditions

Course

Early stage

During the ensuing days the symptoms may show some subsidence and there may be little evidence to incriminate the lungs Occasionally one encounters patients who have actually resumed work, only to be overwhelmed later when the abscess bursts Towards the end of the first week in the typical cases, toxaemia

becomes more apparent, and at this stage a hard, dry, or almost dry, cough, with localized pain in the chest, may appear Such sputum as is produced at this stage is scanty and inoffensive, and is due to inflammation of the bronchi in relation to the abscess.

Rupture

Rupture of the abscess classically occurs about the tenth day of the illness, but great variation is encountered particularly if antibiotics have been used It is preceded, perhaps for 24 hours or more, by the appearance of offensive " fumes " when the patient coughs The actual rupture may be sudden and dramatic, leaving no doubt as to the true state of affairs , in other cases the appearance of sputum is more gradual, but it shows a steady increase in volume during the ensuing few days A small haemoptysis may precede rupture and the expelled contents of the abscess are often blood-stained for the first few days

Course after rupture

Acute cases after rupture —Following rupture there is usually a marked reduction of toxic symptoms although complete subsidence takes longer Cough and sputum will inevitably persist for many weeks until healing has taken place Such is the course of the typical acute case, but it should be emphasized that extreme variation in the clinical course may occur.

Fulminating and hyper-acute cases —Fulminating cases with mounting toxic manifestations may demand surgical relief at an early stage before rupture has occurred, in order to save life, but such cases are rare and have been particularly so since the advent of chemotherapy The hyper-acute case, in which serious symptoms persist after rupture, will also demand early surgical treatment ; the condition is not relieved by discharge of the abscess contents, which is incomplete owing to the presence of large or multiple sloughs in the cavity Such cases require daily (if not hourly) assessment, and surgical drainage should never be withheld when improvement is not occurring Once again such cases are becoming increasingly rare, entirely as the result of the administration of antibiotics.

Convalescence or chronicity —The subsequent course of the typical case varies In those resolving satisfactorily the sputum loses its foetor and decreases in amount after the initial burst This is associated with a corresponding improvement in the clinical condition of the patient Final disappearance of sputum, however, may take several weeks In other cases, cough and sputum persist and a chronic state is reached, in which each day several ounces of purulent sputum are produced These symptoms are associated with mild or moderate toxic changes, such as low-grade fever, sweating, anorexia, weight-loss and the development of finger-clubbing This state of chronic ill-health may persist for many months or even years In other cases, periodic bouts of fever and toxicity and low sputum production alternate with periods of relative well-being and free expectoration of sputum, this alternation suggesting intermittent obstruction of the draining bronchi.

Spread to other organs —Chronic cases, as described above, run a grave risk of spread of the disease to fresh sites in the lung, to the pleura or to the brain These grave and all too frequent complications are heralded by a recrudescence or fresh outbursts of symptoms in addition to those dependent upon the site of the new lesion.

Symptoms

Certain individual symptoms deserve separate consideration

Cough —This is irritating and dry in the pre-eruptive stage and may be particularly exhausting After rupture, however, it is more free, looser and readily productive of sputum; in this stage it is often rather picturesquely described as "fruity"

Expectoration —Prior to eruption the sputum is scanty, mucoid or muco-purulent and caused by an incidental bronchitis in relation to the abscess After rupture of the abscess its character alters markedly, it is now purulent and excessive, often more than 300 millilitres *per diem*, its colour is yellow, green or brown, and it often has the peculiarly penetrating offensive odour which is so characteristic of the condition The sputum is easily raised, often without any effort when it may appear to flow from the patient's mouth With progress towards resolution the volume decreases, the sputum loses its foetor and becomes less purulent and more mucoid Too much reliance should not be placed on the patient's statement about the presence or absence of odour The importance of daily measurement and recording of the volume of sputum produced should hardly need emphasis, but it is too often overlooked It is one of the most important factors in assessing the response to treatment and determining the indications for operation Graphic recording on the temperature chart is the ideal method.

Pain —Pleural pain is usual during the pre-eruptive stage of the abscess, it is often well localized and is due to the fibrinous pleurisy overlying the abscess Pleural pain occurring later should suggest the development of an empyema

Haemoptysis —A small frank haemoptysis may often precede the rupture of an abscess, and the abscess contents are often grossly blood-stained during the first few days following rupture Frank haemoptyses are not uncommon during the later stages and in the chronic cases They form one of the dreaded complications encountered after surgical drainage and are not infrequently so severe as to be exsanguinating and even fatal

Signs

Pulmonary

Physical signs in the lungs are notoriously variable, but areas of impairment of percussion note and diminished breath sounds or bronchial breathing are often detected Added sounds are often minimal in the early stages and later they are not specific Of particular importance in the day-by-day examination of the patient is the elicitation of signs of pleural fluid suggesting an empyema

Extrapulmonary

Pyorrhoea, dental tartar and caries are found in a significant proportion of cases A search should always be made for possible foci in the upper respiratory tract

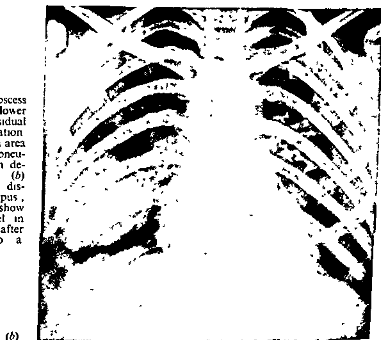
Clubbing of the fingers and toes is common, it may appear early and within a matter of weeks become quite gross Regression, however, usually takes place when the abscess resolves

Radiological appearances

The earliest changes are those of consolidation, which may be segmental, lobar

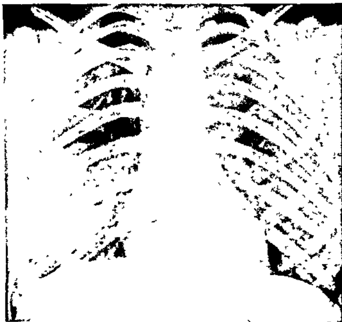


(a)

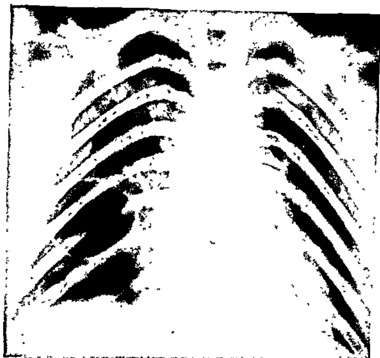


(b)

Fig 90 — Abscess in right lower lobe with residual cyst formation (a) Shows an area of broncho-pneumonia which develops into (b) an abscess distended with pus, (c) and (d) show a fluid level in the abscess after rupture into a bronchus


(c)


(d)



(e)

Fig 90 (*cont*) — (e) Showing a residual "cyst" which remained unchanged for several months

or patchy in distribution (Fig 90) In segmental lesions there may be some shrinkage of the affected area, which is due to associated atelectasis (Fig 84) There is nothing very specific about the appearances at this stage, which would apply equally well to other acute inflammatory lesions With the development of an abscess the affected area becomes somewhat distended and, if it is excessive, a spherical shadow or distended segment will result (*see* Figs 84 and 85) The edge of this shadow is usually hazy and irregular because of surrounding pneumonitis, and it is never clear-cut and sharply defined as seen in a cyst (Fig 91) or a peripheral carcinoma (Fig 92)

With rupture of the abscess into the bronchial tree, air is able to enter the abscess cavity as pus and debris escape, and then a fluid level or an air cap is visible (Fig 90) Sometimes, however, air cannot enter the abscess, owing to the narrowness of the bronchial opening or the presence of a large slough, and a fluid level is then not to be seen It is important to realize that fluid levels are not essential to the radiological diagnosis of an abscess

As the inflammatory process subsides the surrounding consolidation resolves (Fig. 84), the cavity itself usually shrinks in size and finally can no longer be seen, but occasionally it remains little altered in size and, as all evidence of pneumonitis disappears, it assumes a cyst-like appearance (Fig 90)

The frequency with which the posterior segment of the upper lobe, the apex of the lower lobe and the axillary sub-segments of the lobes are involved is mentioned above The anatomical site of the lesion is thus of some diagnostic significance

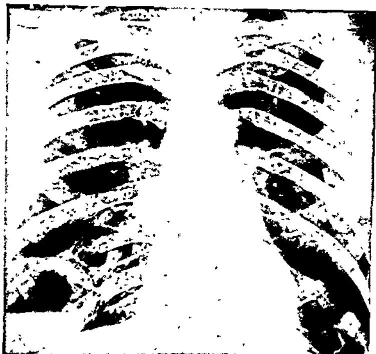
FIG 91 —Large infected cyst in right lower lobe showing the characteristic thin wall with absence of surrounding pneumonitis Treated by lobectomy Specimen revealed a *multilocular cyst* lined by columnar epithelium



(a)



(b)



(*a*)

Fig 92—Breaking down peripheral carcinoma of the right lower lobe showing thick *lobulated irregular* wall



(*b*)

DIAGNOSIS

Investigation

Sputum.—The sputum should be periodically examined and cultured, both aerobically and anaerobically, in all cases. Search should always be made for tubercle bacilli and malignant cells in addition to other organisms. In suspected staphylococcal and Friedlander abscesses, early culture is advised before invasion and contamination by secondary organisms occur.

Bronchoscopy.—The value of bronchoscopy lies in the determination of the cause of an abscess, such as carcinoma or an intrabronchial foreign body. It should be performed in every case which appears unusual in its position, reveals atypical radiological appearances or has an unexpected course, and always before surgery is contemplated. For localization of an abscess it is of less value than good radiography.

Clinical diagnosis

The correct diagnosis is suggested by the elicitation of a history of a febrile illness, followed by the expectoration of large quantities of purulent sputum. The occurrence of foetor and the presence of clubbing provide circumstantial evidence in favour of the diagnosis. Radiography will reveal a localized area of consolidation or an abscess cavity.

Differential diagnosis

There are many conditions which superficially might be mistaken for an abscess, but relatively few which are liable to lead to real confusion.

Differential diagnosis can best be considered from three aspects.

Pneumonic illness

It is emphasized above that the initial symptoms and radiological features of a lung abscess may closely simulate influenza, various forms of pneumonitis, and certain virus infections. At this stage differentiation may be difficult, although a bradycardia, leucopenia, sputum cultures and cold agglutinins may suggest the correct diagnosis. However, the appearances of much purulent sputum should serve to distinguish an abscess from pneumococcal pneumonia, broncho-pneumonia and virus infections.

An empyema following pneumonia may lead to confusion when a broncho-pleural fistula develops at an early stage and results in the expectoration of much pus. Differentiation is often impossible although the x-ray appearances are often of help.

Purulent sputum

Both the chronic bronchitic patient and the bronchiectatic individual are liable to attacks when their symptoms are aggravated. These are often associated with fever and evidence of pneumonitis. The history of cough and sputum preceding the illness is of paramount importance in distinguishing these conditions from a lung abscess, as is also the absence of radiological signs of consolidation or cavitation.

An infected lung cyst may give rise to very real confusion unless, by chance, an earlier x-ray film had revealed the presence of an uninfected cyst or cysts in other parts of the lung. The radiological appearances are those of a clear-cut spherical

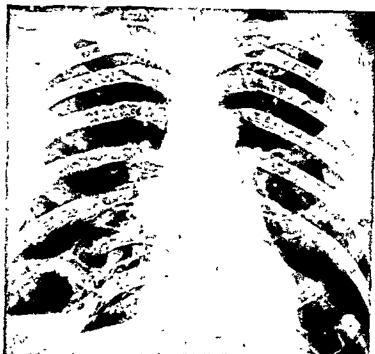


FIG 92.—Breaking down peripheral carcinoma of the right lower lobe showing thick lobulated irregular wall

(a)



(b)



FIG 93.—Large cavity with a fluid level in the right mid-zone. Appearances had remained unchanged for several months. Elsewhere in the lungs there are areas of hard infiltration and calcification but the sputum was persistently negative for tubercle bacilli. Thoracotomy revealed a tuberculous cavity with pus which was teeming with tubercle bacilli. The draining bronchus was completely stenosed

reveal a glistening epithelialized wall with fine spidery blood vessels coursing over it

Hydatid cysts.—In areas where this condition is endemic, recognition is rarely difficult. A positive Casoni reaction, eosinophilia, the occurrence of urticaria and the characteristic radiological signs (Barrett and Thomas, 1944) should leave no doubt as to the nature of the lesion

TREATMENT

Chemotherapy

The sputum should be cultured as early as possible and the sensitivity of the organisms to various chemotherapeutic agents determined. The sulphonamides are usually of little value except in staphylococcal abscesses. Penicillin is effective in the majority of infections, but must be given in doses of approximately 2,000,000 units daily and be continued for a considerable time. Streptomycin, aureomycin and Chloromycetin should be reserved for cases with infection by organisms resistant to penicillin

Physiotherapy

Postural drainage.—Postural drainage is a valuable therapeutic weapon, which employs gravity in order to encourage pus in the abscess to flow into the trachea and main bronchial tree, from whence it can be expectorated. Accurate localization of the abscess by means of postero-anterior and lateral x-ray films enables one to place the patient in such a position that the abscess lies at a higher level

shadow with little or no surrounding pneumonitis (Fig 91). If air is present in the cavity, the wall is seen to be quite thin and sharply defined in contrast to the thicker wall of an abscess With subsidence of infection and disappearance of fluid, the cyst appears as a thin-walled ring shadow. It is emphasized above, however, that cystic shadows occasionally remain for long periods after a true abscess has subsided (Fig 90)

Radiological appearances

There are many [illegible] an abscess, but few which, in [illegible] The condition cannot be di[illegible]y correlation of symptoms and clinical signs Only those conditions which may seriously mimic the disease are considered here.

Peripheral carcinoma.—A peripheral carcinoma has an irregular lobulated outline ; if it is excavated, the central cavity is also irregular and lobulated These appearances are due to the projection of masses of growth into the cavity The wall of the cavity is much thickened (Fig 92) The course is one of slow but steady increase in size

Encysted empyema.—A subacute or chronic encysted empyema may present a well-defined shadow closely resembling that of an abscess Differentiation from an abscess is often difficult, but the following points are useful.

(1) In the lateral x-ray film the empyema shadow is " D " shaped rather than truly spherical, and it is never segmental in its distribution

(2) Clubbing does not occur with an uncomplicated empyema

(3) Expectoration of pus only occurs late when the empyema ruptures into the lung

(4) Secondary contraction of the chest wall is usual with an empyema but does not occur with an abscess

(5) The diaphragmatic outline and costo-phrenic sinuses are obscured in an empyema

(6) Bronchography may be of considerable value in doubtful cases

Interlobar empyema.—This may be particularly difficult to distinguish The empyemas are often secondary to a small abscess and, for practical purposes, behave as such, for they rupture into the lung at an early stage Characteristically the empyema is oval in outline and, when viewed from the lateral aspect, the long axis lies in the direction of the fissure

Tuberculous cavity.—The commonest site of a tuberculous cavity is in the apex of the upper lobe , the presence of infiltration or calcification elsewhere should suggest the correct diagnosis, even when bacilli are not found in the sputum (Fig 93) The sputum is rarely purulent or excessive and clubbing of the fingers does not occur In doubtful cases repeated examination and culture of the sputum, laryngeal swabbing and gastric lavage are advisable.

Lung cyst.—Cysts are briefly considered under " Purulent sputum " above, where it is emphasized that the cyst is spherical in shape, with a clear-cut outline and without any surrounding pneumonitis The wall of the cavity is often so thin as to be barely visible (Fig 91) Should drainage be undertaken, it will be obvious that the cavity is lined by epithelium and not by granulation tissue, and sloughs will not be present in the cavity Following drainage the expected shrinkage of the cavity does not occur, and at this stage inspection of the cavity may

the abscess and the adjacent parietal pleura, that this adherence occurs quite early in the course of the disease and that it may be very localized in its extent

The operation is performed under local anaesthesia in order to preserve the cough mechanism, the abscess is carefully localized by means of postero-anterior and lateral radiographs In difficult cases a few millilitres of a mixture of iodized oil and methylene blue can be injected into the intercostal muscles over the suspected site of the abscess, the position of the " spot " can be checked radiographically whilst the methylene blue will act as a guide at operation (Rabin, 1941)

A vertical incision is made and the selected rib exposed, a 2-inch segment of rib is resected sub-periosteally and the underlying pleura carefully examined If the pleural space is not obliterated a small metal-ring marker is placed in the wound, the depths of which are packed with gauze to promote adhesions The pack can be removed within 7–10 days, when adherence should have occurred and drainage can be carried out

When adequate adhesions are present the periosteum and pleura can be incised with the diathermy knife and the incision extended into the abscess cavity, which, in the majority of cases, lies 1–2 centimetres deeper Once the cavity has been entered, the opening can be enlarged by reaming away a core of lung tissue large enough to permit adequate inspection and packing Debris and sloughs are removed from the abscess and the latter is inspected with a malleable light Particular search should be made for separate loculi, these, if present, should be opened up into the main cavity The intercostal bundle should be ligated at either end of the divided rib and the intervening segment resected The cavity is firmly but not tightly packed with ribbon gauze, soaked in zinc peroxide or some similar cream, whilst the chest wall channel is tightly packed to maintain a reasonable-[illegible]

narrowing of the sinus prevents easy packing

The progress of the case is checked by injecting iodized oil along the sinus every 2–3 weeks in order to determine the size of the cavity and the presence or absence of draining bronchi Drainage must be maintained until the cavity is no longer present and the bronchi are obliterated

Resection

The considerable advance in pulmonary resections during the past decade, together with the advent of chemotherapy, has had important repercussions on the treatment of lung abscess Before the introduction of penicillin, external drainage was the surgical procedure of choice, even though complications directly referable to or aggravated by the surgical procedure were common Complications such as secondary haemorrhage, empyema, spill-over lung abscess, and cerebral abscess were not infrequent Few resections were performed in these cases because complication rates were even higher

The whole picture has now changed, so that resection is, without doubt, the procedure of choice, and external drainage is only very occasionally performed Improved anaesthetic me[illegible]

operative and post-opera

than the pulmonary hilum If the lung is divided into upper, middle and lower zones and each of these zones into anterior, lateral and posterior sections, 9 potential positions for postural drainage are formed To be effective, postural drainage must be employed frequently and for long periods Patients are often only treated for 10 minutes twice daily, with little or no result At least 30 minutes, repeated several times during the day, is a minimum which should be exceeded whenever practicable A period of drainage on rising in the morning and before sleep at night is particularly important Special beds or wooden frames are available for this purpose Children will often sleep in the head-down position in a bed which is raised on blocks Whilst in the drainage position the patient should be encouraged to breathe deeply and to cough to facilitate removal of the secretions

Percussion therapy.—This consists in "hacking and clapping" over the site of the abscess, with the patient in the postural-drainage position This is often effective in dislodging and expelling secretions from the cavity, thus hastening resolution

Ambulation.—The patient should be encouraged to remain out of bed as early as possible, because the additional mobility encourages drainage and helps to maintain good posture and pulmonary function.

Breathing exercises.—These should be carried out in all cases to ensure that respiratory efficiency is maintained Breathing practice can conveniently be given during the periods of tipping, for the exercises and deep breathing encourage drainage

Bronchoscopy

Mention is made above of the value of bronchoscopy as a diagnostic procedure both from the point of view of determining causative factors and for localization of the abscess. As a therapeutic procedure, however, its value is more limited although some authors maintain that it encourages resolution and therefore recommend its repeated performance The average patient, however, has little difficulty in expectorating pus, and it would appear that repeated bronchoscopies are not likely to achieve anything more than will good postural drainage, and will inflict unnecessary discomfort upon the patient

[illegible] which he intro- [illegible] id [illegible] it [illegible] of complete recoveries while the remaining cases are [illegible] penicillin would [illegible] technique, how- [illegible]

Surgical treatment

External drainage

The successful performance of the operation depends largely upon accurate localization The abscess must be approached across adherent pleura ; if a free pleural cavity is transgressed and contaminated an empyema will inevitably result. It is mentioned above that adherence occurs between the visceral pleura overlying



(c)

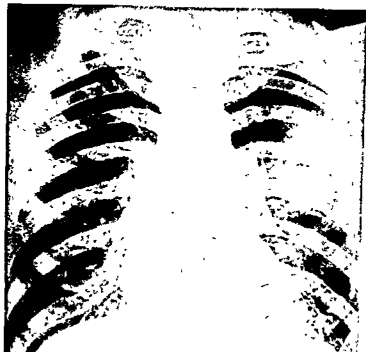
residual dead space, and better surgical technique, have combined to make resection a safer, quicker and more effective method of treatment than drainage

There are, however, certain features of resection for pulmonary suppuration which differ from resections for other conditions In chronic and widespread lesions, the pleura and hilar tissues may be extensively involved, and the resulting fibrosis may present the surgeon with considerable technical difficulties The organisms concerned are often more invasive and potentially dangerous than are those encountered in carcinoma or bronchiectasis, and one finds that septic complications in the wound, in the pleura or in the bronchus stump are a little more common

The management of a case of pulmonary suppuration

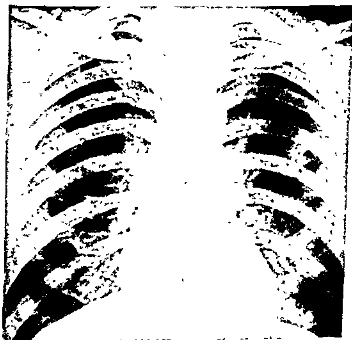
Inadequate and ineffective treatment of cases of lung abscess is all too common It is advisable, therefore, in all cases, whatever the previous treatment may have been, to start treatment as though dealing with a new case This is a policy which can do no harm, yet it has led to cure or marked improvement in a significant number of cases referred specifically for surgical treatment (see Fig 94)

Conservative methods are always given a fair and adequate trial before surgical treatment is contemplated This scheme not only results in a proportion of cures—even in chronic cases—but also provides adequate preparation for cases eventually requiring surgery



(*a*)

Fig 94.—(*a*) Large abscess cavity in the apical segment of the left lower lobe which had been present for 9 months This case was referred for surgical treatment but vigorous postural drainage and percussion resulted in complete resolution (*b*), (*c*) bronchograms revealed only minimal residual damage.



(*b*)


(c)

residual dead space, and better surgical technique, have combined to make resection a safer, quicker and more effective method of treatment than drainage

There are, however, certain features of resection for pulmonary suppuration which differ from resections for other conditions In chronic and widespread lesions, the pleura and hilar tissues may be extensively involved, and the resulting fibrosis may present the surgeon with considerable technical difficulties The organisms concerned are often more invasive and potentially dangerous than are those encountered in carcinoma or bronchiectasis, and one finds that septic complications in the wound, in the pleura or in the bronchus stump are a little more common.

The management of a case of pulmonary suppuration

Inadequate and ineffective treatment of cases of lung abscess is all too common It is advisable, therefore, in all cases, whatever the previous treatment may have been, to start treatment as though dealing with a new case This is a policy which can do no harm, yet it has led to cure or marked improvement in a significant number of cases referred specifically for surgical treatment (*see* Fig 94)

[illegible]

tre

[illegible]

ally requiring surgery

Clinical observations

Proper control of cases being treated can only be made if the following observations are made and duly recorded.

(1) Daily measurement of the volume of sputum, which should be recorded on the temperature chart ;

(2) Postero-anterior and lateral radiography, which should be repeated at least at weekly intervals ,

(3) Bacteriology of the sputum, including both aerobic and anaerobic cultures

Programme of treatment

The conservative programme will consist of the following.

(1) *Penicillin*, in doses of approximately 2,000,000 units daily, or proportionally large doses of such other chemotherapeutic agents as indicated by the bacteriology of the sputum Penicillin should never be discontinued before an adequate trial [illegible] The [illegible]

involve a course of 4–6 weeks

(2) *Postural drainage* and *percussion* therapy, carried out as often and for as long as possible each day. It is impossible to overdo this, but there are patients who [illegible] at first [illegible] Mobility undoubtedly has [illegible]

Assessment of results

[illegible]

x-ray appearances

The following courses may be encountered

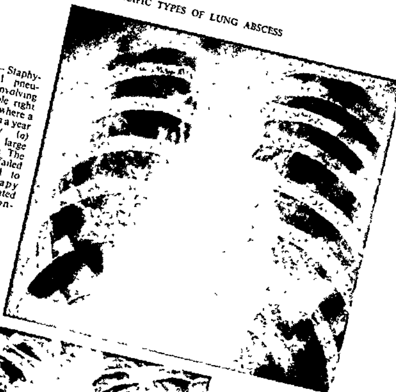
(1) Steady improvement in all aspects of the case, leading to complete resolution with disappearance of sputum and clearing of radiological shadows.

(2) Poor response to conservative treatment these patients should have a resection of the diseased area if the general condition is good and volume of sputum not excessive Toxic cases or those with much sputum will require external drainage

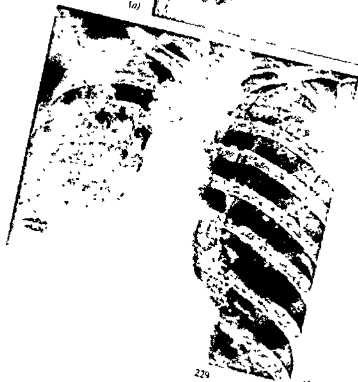
(3) Chronicity or incomplete resolution about 20 per cent of cases reach a chronic phase, in which conservative treatment no longer leads to improvement. Such cases should be submitted to resection

SPECIFIC TYPES OF LUNG ABSCESS

In this section it is proposed to consider some of the distinguishing features of the various types of lung abscess, especially those rega[illegible]eparate entities or as having a distinct aetiology Their recognition may [illegible] be rather academic, but in some instances it [illegible]tical importan[illegible] they require special treatment



(a)



(b)

FIG 95 — Staphylococcal pneumonia involving the whole right lung (b) where a film taken a year previously (a) showed a large basal bulla. The abscess failed to respond to chemotherapy and was treated by pneumonectomy

Specific pneumonias

Pneumococcal or streptococcal pneumonia

These organisms rarely give rise to gross suppuration in the lung and the expectoration of any quantity of pus is unusual The radiological appearances of cavitation, occasionally seen in these cases, probably represent areas where resolution is in advance of that in the surrounding zones

Staphylococcal pneumonia

Of recent years a characteristic type of abscess has been recognized in association with staphylococcal pneumonia Brock (1945) gives a clear and comprehensive account of the condition, and since his description was published many cases have been recognized

A clear distinction should be made between (1) multiple lung abscesses associated with staphylococcal pyaemia and (2) primary staphylococcal pneumonia with abscess formation. In the former the primary focus is often obvious and pyaemic abscesses may be present elsewhere ; the abscesses in the lung are usually multiple, bilateral, frequently small and usually relatively thick-walled

Staphylococcal pneumonia represents one of the local manifestations of "staphylococcal fever", which is a generalized invasion of the body by the staphylococcus In some cases invasion is preceded by a local staphylococcal lesion, such as a boil or infected wound, but in others the local lesion would appear to be in the lung, and a pneumonic consolidation may actually precede blood-stream invasion Such cases are apt to be encountered in lungs which are already the seat of some pathological process , thus influenzal attacks often prepare the way for staphylococcal invasion, and it is often during epidemics that cases of staphylococcal abscess are encountered More chronic lesions, such as bullae, cysts, asthma and chronic bronchitis, may likewise render the lung more prone to invasion by the staphylococcus (*see* Fig 95)

The severity of the case varies considerably, from acute fulminating attacks resulting in death within a few days to the mild case with moderate fever and few symptoms The diagnostic features of the condition are the expectoration of purulent sputum containing staphylococci in pure culture, together with lung cavitation, often giving specific radiological appearances The sputum is purulent, moderately profuse and often blood-tinged in the earlier phases, but considerable variation is encountered Staphylococci are found in the sputum in almost pure culture during the early stages, but later secondary organisms appear and may completely overgrow the staphylococci A positive blood culture is often obtained during the earlier phases of the disease

The x-ray appearances are characteristic and often diagnostic *In the earlier* stages before abscess formation there are areas of consolidation, often lobar or segmental in distribution (Fig 96) The abscesses are characteristically multiple, often bilateral, large, thin-walled, distended spherical sacs, often empty or con- [illegible] encountered even in the same

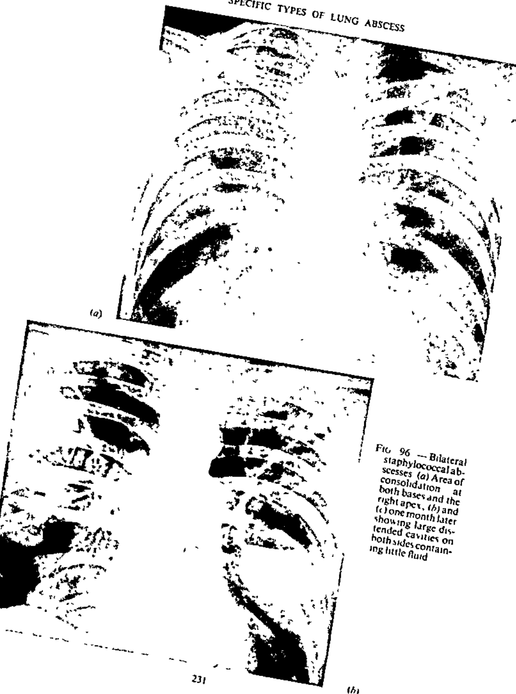


FIG 96 — Bilateral staphylococcal abscesses (a) Area of consolidation at both bases and the right apex, (b) and (c) one month later showing large distended cavities on both sides containing little fluid



FIG 96 (c)

With resolution the distended cavities shrink in size and eventually disappear completely , occasionally one or more may persist as a thin-walled spherical ring shadow, which may be mistaken for a true cyst

Treatment should be essentially conservative with the prolonged administration of large doses of appropriate chemotherapeutic agents The majority of cases which survive the acute phase resolve satisfactorily but patience must be exhibited and treatment maintained for a long time Surgical drainage is not advised and is rarely practicable in view of the multiplicity of cavities Lobectomy or pneumonectomy may very occasionally be indicated if symptoms and cavitation persist in spite of adequate treatment (*see* Fig 95)

Staphylococcal pneumonia in young children

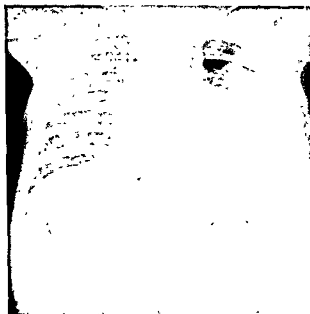
Staphylococcal pneumonia and abscesses are not uncommon in infants and young children and deserves separate consideration Pathologically two types are encountered

Small solitary abscess —In the first the abscess is small, solitary and often subpleural , it frequently ruptures into the pleura producing a tension pyo-pneumothorax (Fig 97) Gross infection of the pleura is rare, however, and usually there is relatively little fluid in the pleural cavity These cases should be treated by repeated aspiration of air and fluid from the pyo-pneumothorax, followed by the instillation of penicillin in doses of 500,000 units This is combined with the systemic administration of penicillin Resolution of the abscess and re-expansion of the lung usually occur readily.



FIG 97 — Staphylococcal pyo-pneumothorax in an infant 3 months old successfully treated by repeated aspirations and chemotherapy The pus grew *Staph aureus* in pure culture (*a*) Tension pyo-pneumothorax with small quantity of fluid, (*b*) partial re-expansion following aspiration, (*c*) complete expansion

(*a*)



(*b*)



FIG 96 (c)

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FIG 98 — Staphylococcal pneumonia with multiple abscesses in an infant 4 months old With chemotherapy toxic manifestations disappeared and the distended cavities became smaller but did not finally disappear for 18 months after the onset

(a)



(b)



FIG 97 (c)

Multiple distended cavitation—In the second type there appears to be a more widespread pneumonic infection, resulting in multiple distended cavities (Fig 98) Sometimes one cavity dominates the picture and may become so large as to mimic closely a spontaneous pneumothorax In fact, it is impossible in many cases to distinguish the two, although ill-advised needling may sometimes give the answer by superimposing a pneumothorax The importance of recognizing these cases lies in their management, which must be strictly conservative It consists in prolonged and adequate courses of the appropriate chemotherapeutic agents, combined with [illegible]

Involvement of an otherwise normal pleura is a risk which would appear justifiable in these cases, and serious sequelae are not common Radiological resolution may take many months, and in some cases may never be complete In such cases radiographs show multiple cystic or bullous changes, and such a condition, if encountered for the first time later in adult life, may well have had its origin in staphylococcal pneumonia in infancy

Actinomycosis

Actinomycotic infection of the thoracic cage or its contents is not uncommon The invasive power of the fungus shows great variation : some cases show steady progression with increasing involvement of all adjacent tissues in spite of adequate

FIG 98 — Staphylococcal pneumonia with multiple abscesses *in an infant* 4 months old With chemotherapy toxic manifestations disappeared and the distended cavities became smaller but did not finally disappear for 18 months after the onset



(*a*)



(*b*)

treatment, whereas others appear to be more benign and easily controlled The majority of cases are secondary to lesions originating in the ileo-caecal region; thoracic involvement is usually preceded by sub-phrenic infection, which in turn is followed by an empyema, pulmonary suppuration and chest-wall invasion. Primary involvement of the lung occurs occasionally and may give rise to pulmonary suppuration with abscess formation; the abscesses are subacute or chronic but often progressive, and involvement of the pleura is common. The fungus is occasionally found in the sputum, but more frequently the diagnosis is made on biopsy material, taken at the time of drainage or resection.

Treatment consists in full and prolonged courses with antibiotics Resection may be practicable in localized lesions, but in extensive cases with an empyema eradication is more difficult (McNab, 1945)

Friedländer's bacillus

Infection of the lung with the Friedlander bacillus usually results in a severe illness with a high mortality The first report of less severe and non-fatal cases was made by Westermark in 1926 Brock (1946) recorded 2 personal cases of the more chronic type, and since then other similar cases have been more widely recognized The chronic forms of infection assume one of two forms: (1) massive consolidation with abscess formation (pseudo-lobar pneumonia); (2) cavitation with fibrosis, closely simulating chronic pulmonary tuberculosis radiologically (Fig 99) Diagnosis depends upon obtaining pure or almost pure cultures of *Bacillus friedländeri* (*Klebsiella pneumoniae*) from the sputum; these may only be found in the earlier stages because they are later over-grown by secondary invaders A correct diagnosis may thus be missed if cultures of sputum are not made early. (Friedlander's bacillus is sometimes itself a secondary invader, so that its appearance with other organisms in the sputum does not of necessity indicate a true Friedlander abscess) An empyema may complicate the abscess, and pure growths of the bacillus may be recovered from the pus

Treatment consists in full courses of streptomycin Some cases prove resistant to treatment and in these resection should be employed if practicable.

Entamoeba histolytica

Lung abscess formation due to *Ent histolytica* is rare, but its occasional occurrence and recognition are important because lesions are usually responsive to appropriate therapy Diagnosis may be made by finding ova or cysts in the sputum or in sections of biopsy material (Harrington, 1930)

Abscess secondary to bronchial occlusion

Complete or partial obstruction of a bronchus invariably gives rise to secondary changes in the lung and bronchial tree distal to the block. Thus, obstructive emphysema, atelectasis, pulmonary suppuration, abscess, bronchial distension and bronchiectasis may all be encountered The factors which determine the secondary changes are (1) the completeness of the occlusion and (2) the nature of any bacterial invasion An ulcerated carcinoma or contaminated foreign body usually results in suppurative changes, whereas an uninfected benign tumour may produce atelectasis without gross infection



[illegible]

Abscess formation due to bronchial occlusion may be difficult to distinguish from other forms, but antecedent chest symptoms, a lobar or segmental distribution of disease and an atypical course or lack of response to treatment should arouse suspicion. The diagnosis is usually readily made by bronchoscopy or bronchography One of the values of routine bronchoscopy in cases of lung abscess lies in the diagnosis of cases belonging to this group

Carcinoma

These cases are caused by tumours arising in the larger bronchi, and the abscess is a distinct secondary manifestation due to suppuration They must not be confused with a breaking-down peripheral carcinoma A preceding history of cough, sputum, and particularly of haemoptysis should suggest the diagnosis which can often be confirmed by bronchoscopy

Treatment is that of the primary lesion Pneumonectomy should be carried out whenever possible and palliative resections are justifiable in this group In [illegible]

[illegible]

drainage of the abscess

Benign tumours—adenomas

Like carcinoma, these tumours may give rise to suppuration and abscess formation in the lung distal to the occluded bronchus On the other hand, infection is often less obvious and severe than in the former group Diagnosis is usually made at bronchoscopy, and treatment consists in the removal of the tumour and the involved lung tissue in as conservative a manner as possible

Bronchostenosis

Stenosis of the bronchus may be due to malignant invasion, tuberculous involvement, trauma or external pressure, and may result in suppurative changes beyond the narrowed or occluded bronchus Treatment will depend largely upon the primary condition

Intrabronchial foreign bodies

Blood clot, inspissated mucus, teeth, fragments of bone, or similar substances may be accidentally inhaled and lodge in one of the bronchi The bronchus is obstructed partly by the foreign body and partly by oedema and granulation tissue Distal to the obstruction the bronchus becomes distended with pus, forming a "bronchial abscess" (Thomson and Negus, 1948) The lung distally may or may not be permanently damaged In the latter case removal of the foreign body combined with chemotherapy should result in complete resolution

The diagnosis is suggested by a history of inhalation of a foreign body, a recent dental extraction or an operation, particularly if the latter has been performed on the upper respiratory tract The diagnosis may be confirmed by bronchoscopy, and removal of the foreign body can often be carried out When this is impossible, vigorous postural drainage and percussion therapy may occasionally dislodge the foreign body, but, should this fail, surgical removal, bronchotomy or resection will be required

Post-atelectatic obstruction

This group requires special emphasis, owing to the grave prognosis if it is not recognized and treated early and effectively

The condition originates in an unresolved post-operative atelectasis; the atelectatic lung is invaded by virulent pathogenic organisms, the invasion resulting in gross suppuration and multiple abscesses The condition is an extremely serious one, and the patient is often gravely ill and toxic, with a high fever and expectorating much foul purulent sputum Spread to other parts of the lung occurs frequently and early, and death from toxaemia and anoxia is common (*see* Fig 100)

Early recognition, followed by prompt treatment of the initial atelectasis by postural drainage and bronchoscopic or catheter suction, should prevent this very serious complication.

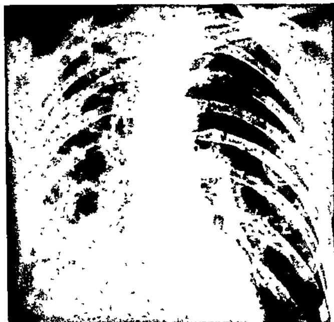


FIG 100 — Post-operative atelectasis with pulmonary suppuration [illegible]

Vascular emboli

Infarct of lung —Uninfected pulmonary emboli rarely give rise to abscess formation but occasionally such infarcts become infected and result in an abscess (Fig 101)

Pyaemic abscess —Lung abscesses secondary to a generalized pyaemia should be readily recognized Repeated emboli will give rise to multiple abscess scattered throughout both the lungs, but occasionally a solitary abscess may be found

Injuries

Haematoma of the lung —Traumatic or post-operative pulmonary haematomas, like infarcts, rarely become infected The usual course results in slow absorption of the blood, but some of it is expectorated Occasionally, however, the haematoma becomes infected either from organisms circulating in the blood stream or from the bronchial tree

Foreign bodies in the lung —Smooth, spherical, metallic or inorganic foreign bodies lying in the lung substance may remain quiescent and unassociated with any



(a)

FIG 101—Infected infarct (a) and (b) two days after the classical story of pulmonary infarction following gastrectomy One week later was coughing up blood-stained pus and film; (c) now shows an abscess cavity.





(c)

infection for long periods Ragged and irregular metallic foreign bodies and

substances may give no clue to their presence on the x-ray film (Fig 102) The previous history of the case may indicate the correct aetiological factor Treatment will consist in resection of the involved area

Non-specific suppurative pneumonia

Approximately one third of all lung abscesses are due to specific organisms or factors, as outlined above The remainder exhibit no such specific characteristics, but they have certain points in common In the past many attempts

particularly that of treatment This division, however, does not appear to be as

the course and prognosis of the two groups are not borne out by present day experience

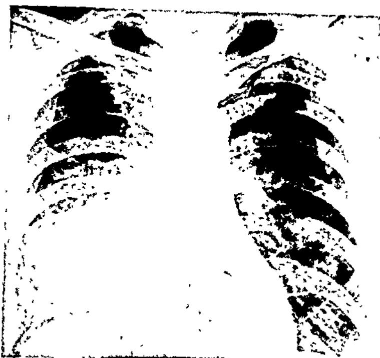


FIG 102 —*Lung abscess secondary to intra-pulmonary foreign body* This patient presented with an abscess in the right lower lobe and was expectorating several ounces of pus daily and having repeated frank

Brock (1945, 1946, 1947) did much to clarify the subject by his clear description

(1950), in an attempt to clarify the subject, has regarded these cases as representing varying degrees of severity of a chronic suppurative pneumonia caused by the inhalation of infected particulate matter That aspiration or inhalation of *infected material is the important factor is supported by the following* observations

(2) A *survey of the anatomical site* shows that the majority of abscesses favour the sites mentioned in (1) above

(3) The finding of dental sepsis, upper-respiratory infections and previous operations in a significantly high proportion of cases

(4) The occurrence of organisms in a lung abscess similar to those found in mouth or nose

Nicholson suggests that the "benign aspiration pnuemonia" of Ramsay a Scadding (1939) represents a relatively benign form of inhalation pneumoni Acute putrid abscess represents a more severe infection, with other cases lying inte mediate between the two and exhibiting varying degrees of suppuration an necrosis.

The "spreading suppurative pneumonitis" of Sellors and his colleagues (1946) can be regarded as an intermediate form, which is prone to acute exacerbation, due to the tendency to spread and involve fresh areas of the lung In 14 of the 27 cases which they describe, infection of the upper-respiratory tract or dental sepsis was present

It seems probable, therefore, that the components of this large heterogeneous group are probably all members of a single basic entity, which Nicholson has termed "non-specific suppurative pneumonia" The various manifestations of the condition depend upon (1) the nature of the aspirated material, (2) the organisms present in the lung, (3) the presence or absence of anaerobic conditions in the involved area, and (4) the occurrence of lung necrosis and sloughing in addition to suppuration

BIBLIOGRAPHY

Allen, D S (1928) 'Etiology of Abscess of Lung, Experimental and Clinical Studies" *Arch Surg*, 16, 179

Barrett, N R (1944) "Lung Abscess, Pathology and Diagnosis of Certain Types" *Lancet*, 2, 647

— and Thomas Dillwyn (1944) "Pulmonary Hydatid Disease," *Brit J Tuberc*, 38, 39

Brock, R C (1945) "Studies in Lung Abscess" *Guy's Hosp Rep*, 94, 115

— (1946) *Ibid*, 95, 40

— (1947) *Ibid*, 96, 97

— Hodgkiss, F, and Jones, H O (1942) "Bronchial Embolisms and Posture in Relation to Lung Abscess" *Guy's Hosp Rep*, 91, 131

Cutler, E C, and Schlueter S A (1926) "Experimental Production of Abscess of the Lung. *Ann Surg*, 84, 256

Harrington, S W (1930) Amebic Hepatic, Subphrenic and Pulmonary Abscesses" *Arch Surg*, 21, 1146

MacNab, G H (1945) Actinomycosis" *Edinb med J*, 52, 219

Metras H and Lieutier, J (1947) 'Treatment of Broncho-pulmonary Suppuration by Local Injection of Penicillin" *Thorax*, 2, 196

Negus, V E (1937) 'Discussion on the Value of Bronchoscopy in Diagnosis and Treatment' *Proc R Soc Med*, 31, 419

Neuhoff, H and Touroff, A. S W (1936) "Acute Putrid Abscess of Lung, Principles of Aspiration Treatment" *Surg Gynec Obstet*, 63, 353

— (1940) "Acute Putrid Abscess of the Lung" *J Thorac Surg* 9, 439

— (1942) *Ibid*, 12, 98

Nicholson H (1950) "Suppurative Pneumonia' *Lancet* 2, 549, 605

Rabin, C B (1941) Precise Localization of Pulmonary Abscess, ' *J Thorac Surg* 10, 662

Ramsay, H and Scadding, J G (1939) "Benign Broncho-pulmonary Inflammations Associated with Transient Radiographic Shadows" *Quart J Med*, 8, 79

Sellors, T H, Blair, L G, Houghton, L E, Thompson, V C, and Pryce, D M (1946) "Spreading Suppurative Pneumonitis" *Thorax*, 1, 146

Smith, D. T. (1927). "Experimental Aspiratory Abscess" *Arch Surg*, **14**, 146.
— (1932). *Oral Spirochaetes and Related Organisms in Fuso Spirochaetal Disease.* London; Baillière, Tindall and Cox
Thomson, St Clair, and Negus, V. E (1948) *Diseases of the Nose and Throat*, p. 140, 5th ed London, Cassell.
Touroff, A S W, and Neuhoff, H (1941). "The Differentiation Between Acute Putrid and Nonputrid Pulmonary Abscess." *J. Thorac Surg*, **10**, 618
Westermark, N (1926) "Ein Tuberkulose Vortauschenden Fall von Friedlanders Pneumonie mit Lange Sich Hinziehendem Verlauf." *Acta Radiol*, **7**, 626.

CHAPTER 10

EPIDEMIOLOGY AND IMMUNOLOGY OF PULMONARY TUBERCULOSIS

THE LATE S ROODHOUSE GLOYNE

TUBERCULOSIS occupies an exceptional if not unique place among the infective diseases It is insidious in its onset and its latent period is almost impossible to define, it may heal without clinical manifestations or it may be protean in its signs and symptoms, and if and when it heals it does so by a process of slow recovery which makes the end point difficult to determine For these reasons it is not surprising that there should be a difference of opinion as to how far one attack protects

Acute, subacute and chronic forms exist, and the chronic form predominates except possibly in the virgin soil of primitive peoples No country of which the people have become infected has succeeded in stamping out tuberculosis It is essentially an endemic disease. It is true that the term *epidemic* has been used in the study of tuberculosis from time to time, but even then it has not the same precision which it possesses in an acute infective disease with a well-defined onset An unusual sequence of cases may, of course, develop in a relatively short time in a tenement, factory or office, but they are generally instances of chronic pulmonary tuberculosis of uncertain origin, and Bushnell (1920) in discussing them considers that only primary tuberculosis should be regarded as occurring in an epidemic form A series of small epidemics of this nature due to bovine bacillus infection in groups of persons previously negative to tuberculin has been recorded in Sweden by Sigurdsson (1945) The clinical picture of these was unusually uniform—an incubation period of 5–8 weeks, followed by fever, malaise, sore throat, dyspeptic disturbances, glandular enlargements, erythema nodosum, conversion of tuberculin test from negative to positive and sometimes a positive gastric lavage finding

WORLD PREVALENCE OF TUBERCULOSIS

Although records of tuberculosis in Europe and Asia can be traced back to the days of antiquity, little information of statistical value is available until comparatively modern times In some countries the clergy used to keep the records of the causes of death, and in England the early Bills of Mortality were compiled from diagnoses made by "searchers" appointed for the purpose Here and there a physician made an attempt to estimate the extent of disease Willan, for instance, gave the causes of death of 245 persons whom he attended during 1795–96, and among these were 77 cases of pulmonary consumption There were no census returns, however, and the only calculation possible was the ratio of deaths from phthisis to the total deaths Analysing this early evidence, Brownlee (1918) showed that consumption was the cause of 15 per cent of the total

deaths in 1631, when the Bills of Mortality began to be recorded, and 25 per cent in 1811. Since that date the disease has steadily declined, from the war periods In Great Britain the first census was taken in 1801 return has been made every 10 years from that date. Registration of became compulsory in 1874, and since then it has been possible to calcu mortality rate.

The compilation of international records of mortality rates was comm by the Health Organization of the League of Nations, and the last serie issued in 1935. Table I below is compiled from the Annual Epidemiol Report issued by the League of Nations (1935), by rearranging the countrie groups according to mortality The figures are deaths from all forms of culosis per 100,000 living It will be noted that many nations made no re

TABLE I

MORTALITY RATES FOR TUBERCULOSIS PER 100 000 LIVING

Under 50 *per* 100,000		*Between* 100 *and* 200 *per* 100,00	
New Zealand	38 8	Lithuania	
Union of South Africa	40 4	Northern Ireland	
Australia	42 5	Spain	
		Austria	
Between 50 *and* 100 *per* 100,000		Irish Free State	
Denmark	51 4	Czechoslovakia	
Netherlands	52 4	Greece	
Canada	60 3	Hungary	
England and Wales	71 8	Portugal	
Scotland	73 6	Estonia	
Belgium	74 8		
Italy	88·8		
Sweden	94 2	*Over* 200 *per* 100,000	
Switzerland	97 1	Chile	

In the United States of America the mortality rate for tuberculosis per 100, living was 47 1 in 1939, and it was reduced to 40 1 in 1945; in 1951 the rate England and Wales was 56·2, Scotland 73 7 and Eire 123 8

These world statistics are a useful index of the prevalence of tuberculosis, it must be borne in mind that they represent fatal cases only. Moreover, standard of diagnosis varies a good deal according to the *facilities availabl different countries* It is essential, therefore, to employ all possible methods investigation in order to arrive at a correct estimate of the extent of the dise These are tuberculin tests, mass radiography, notification of clinical cases seek advice, death certificate registrations, and post-mortem examinations *A com nation of these methods applied to a particular group of persons or to the popu tion of an area* (a tuberculosis survey) is generally accompanied by an inqu also into the causes of the prevalence of the disease When considering grou of cases diagnosed during life it is usual to divide them into classes, (1) *late* active, (2) clinical active, and (3) *inactive.* In the case of pulmonary tuberculos separation into sputum-positive and sputum-negative groups enables the epiden ologist to gauge to some extent the seriousness of the carrier problem, especial if the sputum-positive cases can be further separated into ambulant patien and those in institutions

It is *important to remember* the association of diabetes mellitus and pulmonar

tuberculosis since 1 in 40 diabetics suffer with the disease and since the discovery of insulin and therefore the prolongation of life of diabetics, the world population of persons with diabetes is greatly increased

MORTALITY STATISTICS

Various methods are in use (Registrar-General, 1947) for estimating the mortality from tuberculosis, all of which illuminate the subject from a somewhat different aspect

Total deaths

This is a simple computation of the deaths from tuberculosis at all ages without reservations Table II gives the latest figures available for England and Wales

TABLE II

TOTAL DEATHS FROM TUBERCULOSIS (ENGLAND AND WALES)
(Registrar-General's Statistical Review, 1945)

Age at death	All forms		Respiratory system	
	Males	Females	Males	Females
All ages	13,697	9,767	11,757	7,913
0 -	156	151	34	32
1	544	460	70	74
5	226	228	27	38
10	195	248	53	94
15	534	951	367	755
20	963	1,613	846	1,456
25	994	1,276	913	1 175
30	1,112	1,067	1,026	985
35	1,177	883	1,073	814
40	1,377	681	1,269	609
45	1,329	548	1 251	480
50	1,381	405	1,314	364
55	1 321	367	1,257	311
60	1,119	300	1,067	253
65	726	272	699	222
70	375	181	341	147
75	134	86	120	66
80	26	38	25	30
85	8	12	5	8

Crude death rates

Crude death rates represent the number of deaths per million of the population living, without any corrections Table III gives the figures for males, females and persons in England and Wales in 1945 at all ages

TABLE III

DEATHS FROM TUBERCULOSIS PER 1,000 000 LIVING AT ALL AGES
(From Registrar-General's Statistical Review, 1945)

All forms			Respiratory system		
Males	Females	Persons	Males	Females	Persons
835	449	615	716	364	515

Standardized death rate

The ratio of total deaths to total population as given in the crude death rate may, however, be misleading if the area or country for which it is given has a high proportion of age-groups which are necessarily subject to high death rates. In England and Wales for instance, for more than a generation the proportion of children has been decreasing and persons past the prime of life increasing "Accordingly we must eliminate or make allowance for the age and sex constitution of a population before we can accept the total death rate as a sanitary index" (Woods and Russell, 1936) This corrected figure is known as the standardized death rate, and is the most reliable index of tuberculosis mortality The figures for 1944 are quoted from the Report of the Chief Medical Officer to the Ministry of Health (Jameson, 1946) (Table IV)

TABLE IV

STANDARDIZED DEATH RATES FROM TUBERCULOSIS PER MILLION (Ministry of Health, 1946)

Respiratory			Other forms			All forms		
Males	Females	Persons	Males	Females	Persons	Males	Females	Persons
702	373	528	145	112	129	847	485	657

Proportional mortality

Proportional mortality consists in expressing the deaths from tuberculosis as a ratio of the total deaths from all causes, as set forth in the Table V.

TABLE V

PROPORTIONAL MORTALITY FROM TUBERCULOSIS AT ALL AGES

Deaths, all causes		Deaths, tuberculosis, all forms		Ratio of deaths, tuberculosis, all forms, to deaths, all causes		Deaths, tuberculosis of respiratory system		Ratio of deaths, tuberculosis of respiratory system, to deaths, all causes	
Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
245,436	235,838	13,697	9,767	1 17 9	1 24 2	11,755	7,913	1 20 9	1·29 8

If, however, the number of total deaths is unusually high owing to some exceptional circumstance, such as an influenza epidemic, this method of calculation can be misleading

Autopsy records

Post-mortem examinations in general hospitals provide a better alternative than do death certificates, since the diagnoses are obviously more accurate But a great deal depends on the type of case admitted to the particular hospital. For instance there is a natural reluctance on the part of most public bodies nowadays to admit open cases of tuberculosis to general hospitals unless some means of segregation in a special block or pavilion is available

Again, a clear distinction must be drawn between cases in which the deaths were due to tuberculosis and those in which a small lesion could be regarded

only as a contributory cause or even as a mere incident without significance These autopsy statistics often include also instances of obsolescent tuberculosis, and probably this finding of healed lesions is the chief value of the investigation, since it affords some evidence of the prevalence of infection The figures usually quoted are those of Naegeli (1900) for Zurich, in which he recorded 71 per cent of instances of tuberculosis in all autopsies This figure obviously included both active and healed tuberculosis, but it was compiled many years ago, and the diagnosis of healed tuberculosis in the post-mortem room is largely a matter of personal opinion

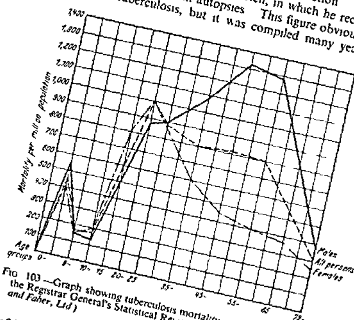


FIG 103 —Graph showing tuberculosis mortality rate by age and sex, from the Registrar General's Statistical Review for 1937 (*By courtesy of Faber and Faber, Ltd*)

This method of calculation has not been much employed in Great Britain The latest statistics are those of Todd (1926) for Edinburgh Royal Infirmary collected in 1926–27 They show 70 per cent of total and 12 per cent of active lesions of tuberculosis

Reviewing all the above methods of assessing tuberculosis mortality, therefore, it may be said that the standardized death rate which is based upon calculations of population and which makes allowance for age distribution is the most satisfactory This is the figure used by the Chief Medical Officer of the Ministry of Health in annual reports

Mortality according to age and sex

Mortality according to age and sex is shown in the graph above (Fig 103) There are really two mortality curves in it which overlap, the one for infancy and childhood, the other for the adolescent and adult The former represents primary

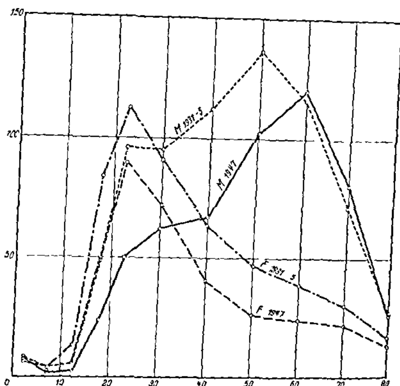


FIG 104—Respiratory tuberculosis in England and Wales. Death rate by age and sex in 1931-35 and 1947 (*By courtesy of "Tubercle".*)

tuberculosis, the latter includes both late primaries and relapses; the former is a mortality curve of acute tuberculosis, whereas in the latter chronic forms predominate; in the former the respiratory forms of the disease are in a minority, and in the latter they account for the major portion of the deaths; the former is either a household or a milk-borne infection except for the rare instances of tuberculosis acquired at school, the latter includes most of the extra-domiciliary cases, the majority of which are attributable to industry. In considering the graph it should be noted too that the lowest section of the curve represents the school-age period; it never again, to the end of the graph, reaches such a low level. The peak of the adult curve is higher in males than in females, but is reached later in life. Several explanations are offered for these facts. Two may be emphasized as particularly important, namely, the slow response of the adolescent-girl group to the general trend of decline in tuberculosis mortality and the serious effect of certain kinds of industry on tuberculosis in the middle-aged and elderly males

Stocks (1949) drew attention to the slower fall in mortality that has occurred in older males in recent years, so that the peak of mortality in males occurred at the age of 60 years in 1947 (Fig 104) Springett (1950) explains this by stating

that if a fall in the mortality rate occurs equally at all ages of cohorts the pea of a peaked curve may shift to an older age period when the rates are studie on an annual basis For any given rapidity of fall in rate the peak of a roundly peaked curve will shift more readily to an older age period than that of a more sharply peaked curve Cohorts are the survivors at any age of all persons born in a given year

NOTIFICATION

Notification of all new cases of tuberculosis in patients consulting the doctors has been compulsory in Great Britain since 1912 It is an attempt to arrive at a sickness rate, but no standard of diagnosis is laid down except that this must not be based on a tuberculin test alone Obviously, diagnosis is more accurate in the chronic respiratory forms of the disease, in which bacteriological and radiological examinations have now reached a high degree of proficiency, than in other forms in which these tests are often inapplicable Annual records of these notifications in England and Wales, from the Report of the Chief Medical Officer of the Ministry of Health, are given in Table VI They are derived from returns made by the Tuberculosis Authorities and are not correlated with population figures The last column in Table VI shows that there are still a good many cases—ranging, in 1944, from 1,133 for non-respiratory forms to 2,335 for respiratory forms of the disease—in which notification was not made before death In other words, the proportion of non-respiratory forms escaping recognition during life was 1 in 8, whereas in respiratory forms it was only 1 in 18 Probably the most valuable contribution of notification is not in its epidemiological record, which is less valuable than the standardized death rate, but the means it affords for early treatment and preventive work, and especially for the timely examination of contacts

TABLE VI

TUBERCULOSIS NOTIFICATIONS AND DEATHS OF PERSONS NOT NOTIFIED
(Abstract from ' On the State of Public Health During Six Years of War ' (Jameson, 1946))

All Ages

Sex	Year	Notifications of respiratory tuberculosis	Notifications of non-respiratory tuberculosis	Deaths of tuberculous persons not notified before death males and females	
Males	1938	21 302	6 511	1 867	Respiratory tuberculosis
	1939	19,605	5,660	1,805	
	1940	20 988	5,272	2,250	
	1941	23,147	5,819	2,872	
	1942	23,623	5,937	2,604	
	1943	24 371	5,750	2,535	
	1944	24,070	5,074	2,335	
Females	1938	16 577	6 299	1,223	Non-respiratory tuberculosis
	1939	15,235	5,616	1,096	
	1940	15,163	5,149	1,145	
	1941	16,352	5,646	1,511	
	1942	17,006	6,053	1,367	
	1943	18,039	6,182	1,245	
	1944	18 824	5,445	1 133	

TUBERCULIN SURVEYS

A positive tuberculin test is a protein hypersensitivity reaction to an injection of old tuberculin into the skin, and it is assumed that a positive reaction thus elicited indicates an infection with the tubercle bacillus, but does not distinguish between bovine-type and human-type strains of the organism. In the early tuberculin surveys (*see* Topley and Wilson, 1943) the technique used was that devised by von Pirquet in 1907, which consisted in placing a drop of undiluted Koch's old tuberculin on the skin and making a scratch through the drop with a lancet. The tuberculin used consisted of a broth culture of the tubercle bacillus from which the organisms had been removed by filtration and the broth then concentrated and standardized. Of late years a purified protein derivative of the culture, known as P.P.D., has been largely used with a graded intradermal inoculation technique generally known as the Mantoux test, although in order to obviate the objection to an injection, especially in tuberculin surveys of children, inunction of tuberculin made up in jelly (Moro's method) or application to the skin of a patch of lint soaked in tuberculin (Vollmer's method) is employed as an alternative. In the graded intradermal test a preliminary injection of 0.1 millilitre of a 1:10,000 dilution of tuberculin is given; if this yields a negative reaction after 48 hours a second injection of 0.1 millilitre of 1:1,000 dilution is given, and, if this again is negative, at the end of 48 hours a third injection of 0.1 millilitre of 1:100 dilution is employed. Although Koch's old tuberculin was originally measured by volume, an arbitrary standard has been accepted that 0.1 millilitre of 1:100 dilution is equivalent to 1 milligram. 'A reddened papule 10 millimetres in diameter at the end of 48 hours is generally accepted as the standard positive reaction. All manner of variations have been employed in the selection of groups of persons on whom to make these tuberculin surveys, and the only conclusion common to them all is that a positive reaction indicates an infection with the tubercle bacillus. It does not necessarily mean activity in the clinical or radiological sense, and, as Rich (1944) has pointed out, we do not know the average duration of tuberculin sensitivity following a slight, well-resisted infection, nor, it may be added, do we know much about the tuberculin reactions of re-infection. Clinical observations on contacts and experiments with B.C.G. and vole bacillus (Wells, 1946) have shown that a tuberculin reaction becomes positive about 6 weeks after infection, and that if no signs or symptoms of disease supervene and if no reinfection takes place repeated tests will give feebler positive reactions until a negative is obtained.' Lloyd and Macpherson (1933) followed up 303 tuberculin-positive London schoolchildren and found that 2 per cent had become negative in two years.

The statistics of these surveys vary markedly in different countries and a different times. The early surveys with the von Pirquet technique in the larg cities of Europe before World War I showed that the percentage of positiv reactors for children of school age (under 14 years) in Prague was over 70, in Par over 80 and in Vienna over 90 (Gloyne, 1944). Rich (1944), however, stress the fact that in most of these early surveys the persons tested were dispensa patients and those in low-income groups. In the modern surveys, on the oth hand, groups of university students and hospital nurses have formed a la

proportion. He gives an instructive table of American surveys made since 1930 which shows that the percentage of positive reactors rises from 0.5 in the 0–1 year age-group to 35 in the 10–14 years age-group, and eventually reaches 95 in the 45–49 years age-group, and remains at that proportion for all other age-groups to the end of life.

Great Britain was comparatively late in the field with these surveys. In the recent Prophit Tuberculosis Survey (Daniels and his colleagues, 1948), a table is given setting forth the results recorded in a number of investigations in England since 1931. These figures relate to adolescents and young adults only, and range from 65 per cent to 92 per cent of positive reactors in the different series. Comparing them with the records of some other countries, the report makes a general estimate for them all of 85 per cent positive reactors in young adult males and 82–83 per cent in females. Most of the series, however, are concerned with student nurses, in whom the proportion of reactors is in some cases exceptionally high; in any case they are a selected group. The work of the Prophit Tuberculosis Survey will be referred to in greater detail below; meanwhile D'Arcy Hart's figures for the London area deserve special attention (D'Arcy Hart, 1932). In 751 patients selected at random from certain hospitals (with the exclusion of suspected or proved cases of tuberculosis) he found that the adjusted percentage of positive reactors with a 1:1,000 dilution (intradermal test) was 6.5 in the 0–2 years age-group, 17 in the 3–5, 30.5 in the 6–10, 60.5 in the 11–20, and 88 in the 21 years age-groups.

The Scandinavian countries have made the most extensive surveys. A number of these are given by Ustvedt (1942). At the beginning of school age (7 years) the Oslo working-class children show fully 20 per cent reactors and the middle-class children barely 10 per cent; at school-leaving age (14–16 years) the curves have risen to 60 and 25 per cent respectively; at 20 years of age to 85 per cent for the working class and 50 per cent for the middle class; and finally at 45 years both groups have attained 100 per cent of positive reactions. These tests were, however, generally made with the von Pirquet reaction. Ustvedt (1942) estimates that half the Service recruits, nurses and students of Norway attain the age of 20 years without being infected with tuberculosis. Investigations in Denmark and Sweden, quoted by Ustvedt, indicate that in these countries infection takes place probably earlier in life. His figures for nurses, students and recruits in France show up to 40 per cent negative reactions, whereas those for Germany (quoted from Redeker in 1937) yielded 30–40 per cent positive at school-leaving age.

Amidst all this the reader may well find it difficult to see the wood for the trees. Opportunities for infection vary greatly according to the social habits of a people. Moreover, it is easy to be misled by the publication of figures compiled from groups of persons, such as nurses, exposed to special risks. One thing, however, seems to be clear. The old view that infection in childhood is the almost invariable rule is no longer tenable, and as a working hypothesis

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reach adult life, and that practically all who attain to middle age will prove to have been infected. In rural areas these figures may well be lower but will depend a good deal on the prevalence of bovine tuberculosis in a district, and the opportunities for the pasteurization of milk.

MASS RADIOGRAPHY

Mass radiography is applied only to radiography of the chest. It began with the use of a full-size film. The most important survey with this method in Great Britain was that made by Wingfield and Macpherson (1936) in 2,381 adolescents, of whom 1,350 were secondary schoolchildren and 1,031 employees in factories and shops. The authors discovered 1·08 per cent of radiological shadows believed to be probably due to tuberculosis and 0.65 per cent regarded as definite. The next phase was the use of a full-size paper film, but very few records were compiled with the method and it soon gave place to the miniature roll film. Extensive use was made of this for the examination of recruits and Service personnel generally during World War II. Workers in this field have, however, adopted somewhat different classifications, so that the statistics are not always strictly comparable. In the United States Army Air Force stationed in Great Britain during World War II, Wayburn (1946) found amongst 77,480 persons 0.08 per cent with active pulmonary tuberculosis, 0.06 per cent with active reinfection type and 0.26 per cent with healed reinfection.

The results of surveys made in the British Forces are shown in Table VII, below, which is compiled from data quoted by Clark and her colleagues (1945), in a Medical Research Council Report.

TABLE VII

INCIDENCE (PER CENT) OF NEWLY DISCOVERED CASES OF TUBERCULOSIS

Service	Tuberculosis			
	Active	*Inactive*	*Doubtful*	*Total*
Royal Air Force (Trail, 1942)	0·22	0.36	0.04	0.58
Women's Auxiliary Air Force (Clive, 1943)	0.34	0.45	0.12	0.79
Royal Navy (Brooks, 1944)	0.72	0.11	0.44	1.27
Women's Royal Naval Service (Brooks, 1944)	0.50	0.41	0.41	0.91

In the same report the authors set forth in detail the results of the first surveys made on civilians in Great Britain. The groups comprised civil servants and the employees of two factories, and a slightly different classification was adopted, those exhibiting significant tuberculous lesions being recorded in two groups, namely, persons who required treatment and persons whose lesions required observation only. Out of 21,280 persons examined at all ages the percentages were as shown in Table VIII.

TABLE VIII

RESULTS OF EXAMINATION OF 21,280 PERSONS (PER CENT)

Sex	Treatment	Observation	Total significant
Males	0.4	1.1	1.5
Females	0.4	0.9	1.3
Persons	0.4	0.9	1·3

The findings in surveys in Northamptonshire and Lancashire have also been published. The former, recorded by Smith (1947), included persons of 14 years of age and upwards volunteering for examination in 4 areas of the county, from factories and offices The incidence of cases of active tuberculosis for all occupations was 4 56 per 1,000 The boot-and-shoe industry, the operatives of which form an important part of the factory population, showed an incidence of 5 85. When this group was excluded the figure for all other occupations in the survey was 3 49 In Lancashire, Bradbury (1947) published the statistics of surveys of 8 factory groups comprising 74,208 persons. He found 239 active and 100 inactive cases of significant tuberculosis, a total of 339, or 4 6 per 1,000. *Of 1,915, or 25 8 per 1,000, cases of non-significant tuberculosis, 400 were inactive* and 1,515 were healed The figure of 4·6 per 1,000 represents cases which were *unknown to the tuberculosis dispensaries*, and Bradbury concludes that in addition to the pulmonary tuberculosis in the general population of which we are aware through the ordinary channels of notification and dispensary organization, there is an approximately equal incidence in those age-groups and sex groups represented by the factory workers, of which we have no knowledge apart from mass radiography He points out that the time of the survey was, of course, abnormal, since so many fit persons were away in the Forces, whilst some of the less fit probably continued at work owing to the urgency of war needs, and he considers that on the whole the annual re-examination of all contacts in the dispensaries would probably give better results 'The most valuable achievement of this mass radiography survey from the public health point of view was the discovery of the sputum-positive symptomless case' It brought to light 1 sputum-positive and 3 early non-infective cases per 1,000 among the groups of factory workers examined

GENERAL TUBERCULOSIS SURVEYS

The various methods of estimating the incidence of tuberculosis described above have concentrated on particular lines of approach such as the recognition of the early symptomless case or the notifiable case or the fatal case A general survey aims at correlating these methods concentrating them on a particular group of persons, and at the same time inquiring into the causative factors believed to be responsible for the prevalence of the disease and drawing conclusions which may or may not apply to the country as a whole A survey carried out shortly before World War I at Framingham, a small town in the United States of America, is generally regarded as having been the pioneer. The most extensive survey made in Great Britain is that of Bradbury (1933) at Jarrow in 1930-31 This town was chosen because it had an unusually high mortality from tuberculosis and occupied an important position in the ship-building industry on Tyneside The neighbouring town of Blaydon, which had a lower mortality, was used as a control At the time of the survey the deaths from tuberculosis accounted for 13 2 per cent of all deaths in Jarrow, 9 3 per cent in Blaydon, and 7 5 per cent in England and Wales as a whole No less than 25 factors were investigated in the course of the inquiry. Most of these earlier surveys concentrated on the environmental factors, which proved to be so many and variable that the later surveys

have been confined to particular groups of persons in which the variable factors were less For the most part the groups selected have been those exposed to exceptional hazards in industry or to special risks of close contact with the disease. In later surveys different methods have been employed in investigating prevalence, for example, sickness and insurance records, tuberculin tests and mass radiography. The most detailed of these in Great Britain are Bradford Hill's work on tuberculosis in the printing trade (Bradford Hill, 1929), Bashford and Scott, 1936), the incidence of the disease in post-office workers (Bashford and Scott, and medical Prophit Tuberculosis Survey (1948) of hospital contacts (nurses and medical students), and the research at present being carried on in the boot-and-shoe industry by Stewart and Hughes (1951)

The inquiry made by Bradford Hill (1929) into the printing trade covered the years 1921–25 The adverse position of the workers in this industry with regard to respiratory tuberculosis was not nearly so distinct in the period 1921–23 as it had been in a previous period 1900–02, but it was still definitely in evidence An analysis of 30,000–40,000 National Health Insurance records in the different occupational groups of the industry showed that this abnormal incidence of pulmonary tuberculosis was derived at least in part from compositors at the beginning and end of insured life and from machine printers in late insured life. In the case of compositors it was tentatively suggested by the author that the composing room was possibly attracting an undue proportion of the less physically robust

TABLE IX

MORTALITY RATE OF PRINTERS FOR 1900-02, 1910-12, 1921-23
(*Expressed as a percentage of the mortality rate for all males*)

Period	Cause	Ages 15–	20–	25–	35–	45–	55–	65–	75 and over
1900–02	All causes less tuberculosis	105	90	70	71	91	92	92	87
	Tuberculosis	175	214	166	170	135	144	115	52
1910–12	All causes less tuberculosis	90	85	71	78	89	90	94	84
	Tuberculosis	129	186	148	142	142	128	158	103
1921–23	All causes less tuberculosis	109	91	100	85	92	102	98	
	Tuberculosis	206	124	122	120	119	147	171	

By way of comparison may be quoted the experience of the General Post Office, although the largest employer of labour in the country, does not experience as a whole any special risk Bashford and Scott (1936) draw 'the following conclusions from their examination of 3,755 cases of pulmonary tuberculosis occurring during a period of thirteen years and observed for a period of not less than te years First, of those who develop pulmonary tuberculosis, not more tha 50 per cent return to work Secondly, amongst those who return, there is ultimate a further wastage of about 48 per cent as a result of recurrent pulmonary tub

culosis or other forms of ill health Thirdly, of cured and arrested cases which survive a period of ten years, the wastage is reduced to about 14 per cent Lastly, light manual or clerical indoor workers would appear to have a slight advantage over manual mainly outdoor workers, and a 10 per cent advantage in respect of subsequent survival after resumption of duty.

Stewart and Hughes (1949, 1951) studied the results of miniature mass radiography in Northamptonshire and found that the incidence of newly discovered active disease in 1945–46 was higher in the boot and shoe factories than in other industries in the county. In the boot and shoe industry this type of case was found as often among men as among women, whereas in other occupations women were chiefly affected They also found the case incidence was higher in large than in small boot and shoe factories and higher for checkers, lasters, and finishers than for rough stuff workers

TABLE X

PULMONARY INCIDENCE IN BOOT AND SHOE FACTORIES ACCORDING TO NUMBER OF WORKING POPULATION

Size of working population	Pulmonary tuberculosis rate per 1,000
1–100	3 1
101–200	5 2
201–350	6 2
351–600	7 4
Over 600	10 1

They concluded that certain types of work suit the requirements of physically handicapped persons, and that this applies to the boot and shoe industry which in 1945–46 was employing an exceptionally large number of previously notified cases, chronic undiagnosed cases and acute undiagnosed cases When these were controlled and a second survey carried out in 1948 the incidence of newly discovered

other rough stuff workers partly because their work is relatively heavy and partly because they are more widely spaced than other workers

The Prophit Trust Survey was concerned with 5 groups of young adults : (1)

is, a group

(3) medical

The nurses

were divided into 2 subgroups . (a) from hospitals admitting all classes of patients including the chronic sick and advanced types of many diseases and having tuberculosis wards for advanced and open cases ; and (b) from hospitals which were more selective in their admissions, had no tuberculosis wards, enjoyed a more generous bed-spacing in their wards and recruited few Irish and Welsh nurses, who generally show a lower natural resistance. All persons included

in the survey were volunteers. Altogether 10,000 young people were examined in the survey. They were all presumably healthy on the first examination, they were drawn from various sections of the population and they were re-examined at regular intervals for varying periods. In the group of navy boys the mean age was 16 years, in the nurses, medical students and controls it was 21 years. Most of them were English from urban areas with the exception of the hospital group (a) nurses, which group had a relatively high percentage of Irish and Welsh from rural areas The results of the tuberculin tests have already been referred to A radiological examination on entry into the survey revealed that 0·5 per cent had lesions which were considered tuberculous and probably active, and nearly 1 per cent showed evidence of inactive "reinfection" tuberculosis and from 5 per cent to 9 per cent calcified foci The incidence of visible pulmonary lesions was highest in country girls who had spent a year or two in an urban district before entering the survey.

Many obstacles were encountered in carrying out the survey in war-time and it was not found possible to do all that was planned, but the investigation is the most thorough so far undertaken in Great Britain on hospital nurses. A valuable summary of the survey has been written by Jacobs (1948) in which he stresses the fact that it is a record of tuberculosis in certain middle-class groups; no survey of industrial workers was attempted

TUBERCULOSIS IN INDUSTRY

The Industrial Revolution is generally regarded as having commenced about 1760 with the invention of steam power and various mechanical devices for increasing production (for example, power looms, carding engines and new types of spinning frames) and to have been completed by about 1840 when Parliament had become sufficiently alive to what was happening to introduce special Acts for the control of industry. During this period tuberculosis is believed to have been rife in the newly built-up industrial areas, though the mortality in the old-established rural districts was probably little affected At the end of the Industrial Revolution the mortality was probably in the region of 200–300 per 100,000 living, but no really reliable figures exist, least of all figures dealing with industry. Collis (1923) lays down the following general rules When a country begins to change over from agricultural pursuits to industry a rise in tuberculosis mortality takes place in the young adults of the new industrial areas, especially among the males As industrial conditions become stabilized the peak of the mortality recedes to the later age-groups; then the rate begins to fall and finally, in well-organized areas, may reach a lower level than in backward rural districts At the same time certain industries stand out as having a higher incidence than that of the general population, by reason of their special risks, though the old phrase "the tuberculosis-ridden industries" happily no longer applies to Great Britain. The "dust-hazard group" bears the greatest share in industrial tuberculosis [illegible] 600 per 100,000 living [illegible] ws the position in other [illegible] tality rates per

100,000 living, the figure 100 being taken as the standard for all males The occupations have been rearranged in order of gravity

TABLE XI

INDUSTRIAL TUBERCULOSIS STANDARDIZED MORTALITY RATES PER 100,000 LIVING

*Warehousemen (textiles)	364
Metal glaziers, polishers, moppers and buffers	230
Barmen	212
†Boot and shoe operatives	188
†Dock labourers	186
*Waiters	178
Hairdressers	162
*French polishers	148
Innkeepers	148
*Iron and steel foundry workers	139
General labourers	13[illegible]
Salesmen and shop assistants (textile and clothing)	12[illegible]
Road transport (horse-drivers)	12[illegible]
Paperhangers and painters	1[illegible]
†Metal-moulders and die-casters	1[illegible]
†Building trade operatives	1[illegible]
Retail salesmen (dairy, meat, fish and greengrocery)	[illegible]

* Wives also show a probably significant excess mortality
† Wives also show a significant excess mortality

The significant and probably significant excess of deaths in the wives of cer groups is important since it raises the question, recently stressed by Stewart Hughes (1949), as to how far the excess mortality is due to faulty industrial co tions and how far it is attributable to housing and family contact in the wor

Excluding the dust hazard group, Collis (1923) classifies the workers with tuberculosis risks into 2 groups, (1) those with special risks of expos predisposing causes of tuberculosis such as chronic alcoholism (barmen), irr employment (dock labourers), open-air work in all weathers and in bad con generally (costermongers), and (2) those which tend to recruit the less ph fit because a robust physique is not essential (printers, boot-and-shoe op clothing workers and warehousemen)

TUBERCULOSIS IN TIME OF WAR

There are many reasons why the mortality from tuberculosis should ris time, it is an inevitable consequence of the dislocation of social life an In previous wars it was difficult to express the rise in figures because men went to the war and the rest of the population stayed at home, over-all figure was difficult to obtain World War II, however, was in that the risks, privations, overcrowding and food deficiencies fell batant and non-combatant alike Collis (1922) noted two features in mortality in Great Britain in World War I—a rise in the young adu the munition areas and a general rise for the whole population in of the war, when an influenza epidemic, which fell hardly upon th swept the country There was no epidemic of this kind in World Great Britain air-raid shelter life, evacuation of the population fr ...d the closure of sanatorium beds caused a rise in the mo ...ring the first 2 years, as will be seen fron

TABLE XII

TOTAL TUBERCULOSIS DEATHS, 1938–42

1938	1939	1940	1941	1942
25,539	25,623	28,144	28,670	25,444

By the middle of World War II the situation had righted itself, but this was not so in the devastated area of Europe, where the conditions remain extremely serious A report made by a group of physicians working under the auspices of UNRRA [illegible]
tior [illegible]
fror [illegible]
the [illegible]

DECLINE IN TUBERCULOSIS MORTALITY

The general decline in mortality may be attributed to a general improvement in preventive medicine and hygiene and in social conditions during the last century and to the direct attack on tuberculosis since the discovery of the bacillus in 1882. As noted earlier in this chapter, statistics before the middle of the nineteenth century are not entirely reliable In a detailed survey D'Arcy Hart and Payling Wright (1939) have shown that (1) during the latter half of the nineteenth century there was a steady decline in phthisis mortality in every age-group, (2) about 1900 a check took place in this improvement and the subsequent decline in mortality has been slower; (3) a further setback occurred in World War I; and (4) the retardation of the rate of decline has been most marked in the young adult age-groups. Expressed statistically, Heaf and Rusby (1948) note that the annual rate of decline during the 60 years period 1851–1910 was less than 1 per cent, and during the period 1911–46, which includes two devastating wars, it was nearly 2 per cent

INFECTION

Portals of entry

The respiratory and digestive tracts are the common routes of infection. Invasion by the skin is confined to a very small number of persons who handle tuberculous material, and even lupus is nowadays regarded as a haematogenous spread, and direct genito-urinary infection is a bacteriological curiosity. At the beginning of this century pathologists were divided as to the relative importance of the respiratory and digestive tract portals of entry, but the work of Cobbett (1917) followed by that of Scott (1930) and Blacklock (1932) has left little room for doubt that as far as post-mortem evidence goes the respiratory route is the commoner.

Tubercle bacilli may reach the digestive tract through food or as a contamination of crockery and table utensils or by way of unwashed hands (for example, after the sorting of soiled linen) In the case of the respiratory tract, two possibilities are recognized · (a) the presence of tubercle bacilli in the dust of rooms used by tuberculous persons; and (b) the adhesion of bacilli to fine droplets of saliva or nasopharyngeal secretion disseminated in the air by coughing or sneezing. This so-called "droplet infection" is generally regarded as the

commonest means of disseminating bacilli. The droplets may travel 40–50 centimetres through the air. Saliva is believed to have only a feeble bactericidal action, and little is known of the effect of mucus. Gastric juice, too, must be a weak bactericidal agent, for tubercle bacilli can be cultivated readily from stomach washings, and Inkster and Gloyne (1921) failed to demonstrate any bactericidal effect on the bacilli by using measured portions of fractional test meals. Owing to technical difficulties and anatomical differences of vascular and lymphatic distribution in the lung, experiments on the portal of entry in domestic and laboratory animals have been inconclusive. Two points, however, may be emphasized, namely, that regurgitation of infected food from pharynx to trachea is by no means infrequent and that natural contact between experimentally infected and healthy animals probably takes place by both routes.

Dose

It has been somewhat rashly claimed that a single bacillus is sufficient to produce disease in the guinea-pig, but, whatever the figure, it is clear that small numbers suffice to infect this very susceptible animal. The lesion produced by small doses is different in character from that produced by large ones. But we know very little about the size of the dose in man, and the experimental evidence in animals helps us little. There is an old maxim that large doses infect and small doses protect, but massive infection is probably very rare, and nowadays most immunologists are inclined to the view that in the great majority of cases the invading force *is* a small one. Here there are two divergent views. The older and more generally accepted conception is that of a small repeated dose, but a new suggestion has been made of late, namely, that because the primary focus is often single, therefore the infecting dose must have been single also. Experimental work by Chaussé (1916) and Bruno Lange (1924, 1931) is generally cited in support of the single-dose view, and is quoted in some detail by Ustvedt (1948). With the use of sprays and sharply bent tubes these authors showed that it was not possible for infected droplets or dust particles of more than 10–15 microns diameter to reach the alveoli, and they held that the number of bacilli adhering to these small particles must be very small, in fact only a few bacilli—the "infectio minima" of Lange. These figures on the size of the saliva droplets are not altogether consistent with observations on the pneumoconioses, in which dust particles of 30 microns and more in their shortest diameter have been found in the alveoli.

Experimental work on guinea-pigs seems to indicate that smaller doses infect by way of the respiratory tract rather than by the digestive tract. Here again the matter is not capable of proof in man, but some important data were obtained from the Lubeck disaster. A group of 251 newborn infants were given 3 doses of B C G vaccine by mouth during the first 10 days of life. Clinical tuberculosis followed in some cases within a few days and it became evident that a virulent strain of tubercle bacillus had gained access to the vaccine as an accidental contamination. In all 72 infants died and the interval which elapsed between the administration of the vaccine and death varied in a remarkable way from 2 to 498 days. Primary foci were found at one or other of the following sites: (a) mouth and middle ear, (b) pharynx, oesophagus and stomach, (c) small intestine; and (d) lungs. The order of frequency was small intestine 98·3 per

cent, mouth 78 3 per cent, lung 20 per cent, and oesophagus 18 3 per cent, bu the majority of the cases more than one primary site was discovered. impressive fact is that in an infection which was known to have taken place by v of the digestive tract there were *no less than 20 instances of primary foci in* lung It seems probable that this was due to regurgitation of the vaccine into respiratory tract during its administration This has been found to occur a *in calves experimentally fed with infected milk*

Carriers

The tuberculosis carrier is obviously in a different category from the carr of an acute infective disease He is not a healthy person harbouring tuber bacilli but one whose disease, though active, enables him to go about among fellows whilst expectorating tubercle bacilli Generally speaking, there are t types of such persons (a) those who are suffering from an early, unrecognize almost symptomless lesion with a small amount of sputum which is regarded merely the outcome of a mild catarrh , and (b) diagnosed cases who are passi through an ambulant, generally apyrexial phase, but who still have a positi sputum More persons in the first group are now being discovered, as a resu of the miniature mass radiography surveys The second group is larger than should be owing to the lack of sanatorium beds Lastly, recent laryngeal an *bronchial swabs* have increased the number of bacillus-positive cases in bo groups until it is difficult to say at what stage a patient becomes or ceases to b infective It is probably safe to assume, however, that the risk of infection *negligible—except for infants and young children—in a person in whose sputu* tubercle bacilli have not been found in direct films on three successive tests.

Contacts

Fortuitous contact with tuberculous persons for short periods must take plac with all of us in daily life, and such contact is for the most part unimportant *The term should be reserved for frequent contact with an open case of tuberculosi* for some weeks or months. Under what conditions this infection takes place and why some persons escape and others fall victims when living in the same environment we do not know *Personal habits* and *individual variations* in resistance are probably important factors Four classes of regular contacts may be recognized : (a) familial or domiciliary ; (b) hospital ; (c) extra-domiciliary groups such as those in schools, factories, and other institutions; and (d) farm and cattle contacts.

... has been recognized since Sir Robert Philip ... 1887 It must be borne in mind ... ation of the family and the home ... essarily the first or original case giving rise to the infection of the household, and it is customary nowadays to sp ... the "index case"

... those under 5 years of age

W. ... ination in France he stated that no less than 24 per cent of the children born into tuberculous households in Paris died of the disease *No other writer has confirmed these striking figures.*

The English figures collected from various sources by Kayne (1937) before World War II showed a mortality ranging from 1 7 per cent to 5 2 per cent in households where there was a sputum-positive case In Lancashire, Lissant Cox and his colleagues (1929) found 50 deaths from tuberculosis in 1,486 children. In these the deaths were distributed as follows 31 meningeal, 8 generalized, 5 pulmonary, 4 abdominal, 1 bone and joint, and 1 glandular tuberculosis Attention was then turned from mortality to tuberculin statistics Heaf and Rusby (1948) have collected the most important of these Dow and Lloyd (1931) at Brompton Hospital found that 71 4 per cent of children under 5 years of age who were exposed to a sputum-positive case in the home gave a positive reaction, and Opie (1935) in America records 75 per cent Following up his cases, Opie noted that in those of which he was able to obtain records up to 15 years afterwards, a period of 10–14 years elapsed between the time of contact and the development of tuberculosis Finally, Dow and Lloyd concluded from their figures that in an average working-class household the mortality from tuberculosis amongst children in the first year of life was more than twice as high in exposed as it was in unexposed households A tuberculous mother is generally the infecting agent in the infants under 1 year old , after that the father is the greater source of danger Miniature mass radiography is now emphasizing once again the importance of domiciliary infection, and it is difficult to determine what are the practical limits of case-finding Two types of contact should be distinguished those which are discovered on the first examination after the notification of the index case and those which are found in a subsequent follow-up of the family A recent Medical Research Council memorandum has suggested that in the case of young adults skiagrams of the chest should be taken at 3-monthly intervals and the patients kept under observation for at least 2 years after the contact has been broken All workers are agreed that the children, the adolescents and the young adults are the most important members of the family to keep under observation

Before leaving this subject reference must be made to childhood infection in village settlements for the tuberculous An investigation by Cox, Heaf, McDougall and Powell (1942) on 204 families in a population of 996 persons resident in a colony for from 2 to 18 years showed that there had been not a single death among the children Brieger (1944) at Papworth found, in a radiological survey of 108 children born in the village, that 51 per cent exhibited nothing abnormal, 43 per cent calcified foci, 46 per cent primary lesion and 1 9 per cent a transient perifocal reaction Heaf and Rusby (1948) in summarizing the figures from the village settlements, quote effectively Bardswell's remark that if the principles of the settlements could be translated into everyday life there would be little to fear

Statistics relating to contact infection between husband and wife are not convincing They show that when one partner is tuberculous the other becomes infected in from 2 5 per cent to 6 4 per cent of cases, but these figures, which are taken from records in various countries, are not recent and there is reason to believe that this risk is not now so great as it used to be Early marriages are common than formerly and the older the partners, generally speaking, the greater the risk The danger of the husband infecting the wife is said to be greater *vice versa*.

Hospital contacts

Among the hospital contacts the nurse has naturally attracted the most attention. Observers seem to be agreed that she runs a greater risk than do her sisters who do not nurse but how much greater this risk actually is no epidemiologist has been able to determine with accuracy. This is not surprising because the methods of appraisement have radically changed. We began years ago noting the number of clinical breakdowns during training. Then, realizing that tuberculosis might remain undetected for many months, the inquiries were extended to at least a year after the nurse had left hospital. Next, the tuberculin test came into use, and, finally, the serial skiagram and miniature mass radiography.

Before the use of tuberculin tests and radiological examination, records of breakdowns from the disease amongst nurses in tuberculosis institutions in England were collected by Squires. In a nurse population of 234 there were 3 breakdowns (1·2 per cent). In 1926, statistics from the Welsh National Memorial Association showed 11 breakdowns (1·1 per cent) in a nurse population of 996. Thereafter records have been published from many countries which have shown that the breakdowns varied from 1 per cent to 6 per cent, according to the local conditions and the searching character of the inquiry. Of these, one of the most impressing is that of Carmalt Jones (1933) in New Zealand shortly before World War II. He found that 3 per cent of the nurses became clinically tuberculous before their training was completed, whereas the girls from the same social grades who joined the Hospital School of Massage, the Home Science School of the University and the School Teachers Training College had had a much better record. During the period of inquiry, only 2 cases of tuberculosis occurred in these 3 institutions with a total student population of 1,125.

Tuberculin tests in nurses were initiated by Heimbeck (1938), and his figures for the Oslo hospital have become the yardstick of all similar inquiries. He found that the incidence of breakdowns among nurses who were tuberculin-positive when joining the staff was 1·4 per cent, whereas it was 22 per cent among those who gave a negative reaction on arrival. Topley and Wilson (1943) however, pointed out that some of these positives were cases of erythema nodosum which may not have been tuberculous. Since Heimbeck's work numerous other records have been published emphasizing the same point, but the figures in these have not been so striking. It seems clear, therefore, that practically all student nurses become tuberculin positive before the end of their training but only a small proportion produce active lesions of tuberculosis necessitating treatment, and that the percentage is greater in those who start with a negative reaction.

Attention was next turned to the serial skiagram. This is a more reliable method of investigation and has been used effectively in the Prophit Trust Report (1948) referred to above. But in spite of all these investigations it is still extremely difficult to ascertain the facts, and only a follow-up survey for at least a year after the completion of training in those hospitals which have maintained a regular tuberculin and serial radiograph service during the whole of the nurses' careers will give us the answer. The following tentative conclusions can, however, be drawn as far as the conditions in Great Britain are concerned. (i) The sanatoria have good records, and for the most part the prejudice against sanatorium nursing

as a risky occupation is unfounded (ii) The undergraduate teaching hospitals come next; they recruit a higher proportion of student nurses with good resistance and have a higher standard for entrants, they usually have no tuberculosis wards and do not wittingly admit cases of chronic pulmonary tuberculosis (iii) Those general hospitals part of whose duty it is to care for the chronic sick and for the dying cases of tuberculosis are less well placed (iv) Student nurses from the country districts of Wales and Ireland generally have a lower resistance to tuberculosis than have those from the English towns and villages (v) There is such a wide variation in the environment in which the nurses work and live in the different hospitals that an accurate over-all picture of the prevalence of tuberculosis is almost impossible to obtain The Prophit Trust Survey shows that when expressed in terms of annual morbidity rates per 1,000 of the population, the figures for English nurses range from 9 7 to 13 7, as against 5 5 for controls

The medical student is in a different category from that of the nurse His contact with the patient is less intimate, he does not live in hospital, his opportunities for open-air exercise are probably greater, his curriculum allows him more latitude, and nowadays he generally begins his ward work at an older age than does the student nurse He ought therefore to have a better record In the Prophit Trust Survey statistics quoted above, the figure for medical students was 9 9. In other words, the medical student who spends the greater part of his clinical training in a teaching hospital has a record similar to that of the student nurse in the same type of institution, in spite of his greater advantages as regards intimate contact with the patient

Until quite recently the record of mental hospitals was unsatisfactory, and in some quarters the view was held that mental patients as a class possessed a low resistance This has not been satisfactorily demonstrated, but it does seem obvious that opportunities for contact infection in institutions composed largely of uncooperative persons must be considerable Some time after World War 1 Evans (1943) showed that in the mental hospitals of Great Britain the crude mortality figure for all forms of tuberculosis at the end of that war had risen 51 8 per 1,000 resident, and that of phthisis was 45 6 Thereafter the figures slowly declined until in 1927 the ratio of the mortality from pulmonary tuberculosis in mental hospitals to that of the general population was 10 1 to 7 2 In other words, Evans found that the mortality in these hospitals had been reduced by some 40 per cent Recent mass radiography statistics compiled by Heaf and his colleagues (1947) in the London area indicate that there has been a still further improvement

Evans had originally noted that the types of mental disease in which the mortality was highest were those of the congenital defective and of primary dementia groups

Institutional contacts

Of the institutions other than hospitals the school is probably the most important. In a memorandum issued by the Joint Tuberculosis Council 8 examples are quoted in which an adult proved to be an infective case in institutions for children where cases of childhood tuberculosis had occurred In 6 a teacher was found to be the source of infection, in 1 it was an adult member of a religious order in charge of an orphanage, and in 1 the source was 2 adults living in a hostel

for unmarried mothers with babies A ninth example is cited of a mass radiography survey of 1,084 teachers in an industrial city, of whom 11 were found to have tuberculous lesions (3 with active disease, 2 of them with positive sputum) The memorandum concludes with the opinion that the chance of infection of children diminishes on the following scale: tuberculous households—nursery school or children's home—elementary and rural schools—large schools in urban areas.

Factory contacts

The prevalence of tuberculosis in the workers in certain types of factory and workshop, notably those with a dust hazard, is undoubtedly high, but the evidence for contact infection is still incomplete, and no reliable figures are available The mass radiography figures do not distinguish between workers infected at home and those infected in the factory.

Cattle contacts

Apart from the infection of man with the bovine bacillus through milk, there is a small collection of records by Griffith (1937) which shows that in agricultural areas farm workers may become infected in the course of their work in handling tuberculous cattle The danger is greater probably in handling dairy cows, which may excrete tubercle bacilli in nasopharyngeal and uterine discharges, in faeces, and in urine as well as in milk.

RESISTANCE

Resistance to the tubercle bacillus is to some extent conditioned by the strain of the infective organism, and there are many species of bacteria within the family mycobacteria The following are the main species. (1) a strain affecting cold-blooded animals (for example, frog, turtle and reptiles) but not found in man; (2) an avian strain of which only some 20 or more cases of infection in man have been recorded in the world's literature, (3) a small rare group of assorted strains of low virulence isolated from human lesions but not conforming to standard strains, (4) the bovine strain affecting man and the domestic animals; and (5) the human strain which affects man, the ape and very occasionally other domestic animals The distribution of the bovine and human strains is given in Table XIII, adapted from Topley and Wilson (1943)

In studying the resistance of man to tuberculous infection the time sequence [illegible] Basing their arguments on tuberculin reactions and the radio-

[illegible]

never dies out (endogenous), others assume a [illegible] (exogenous). If we accept the positive tuberculin reaction as the starting point it seems reasonably clear that the age of infection is moving from childhood to the early adult years How far this is due to lessened opportunities for contact and how much can be attributed to increased resistance is not so clear. We are in fact now looking at a pathological picture which displays five types of lesion: (1) a childhood primary focus which heals; (2) a childhood focus which goes on to dissemination of bacilli and death; (3) a childhood type which smoulders

TABLE XIII

DISTRIBUTION OF HUMAN AND BOVINE STRAIN OF INFECTING ORGANISMS

Animal	Strain	
	Human	Bovine
Horse	O	+
Ox, goat, pig	∓	+++
Dog	±	±
Pig, rabbit	±	+++
Man	++	++
Ape, guinea-pig	+++	+++
Rat, mouse	Y	Y

O = Practically insusceptible
∓ = Local retrogressive lesion
± = Local tuberculosis at site of inoculation with occasional slight dissemination
+ to +++ = Increasing degree of susceptibility
Y = Chronic extensive, generally non fatal tuberculous septicaemia without true caseous lesions (sometimes known as the Yersin type of tuberculosis)

on to adult life, (4) a primary lesion in an adult known to have been previously tuberculin negative, and (5) a healed childhood lesion with an adult lesion suggesting reinfection The last is the most equivocal issue and brings us face to face with the question whether, as D'Arcy Hart (1932) has put it, the extinction of infection is followed by complete loss of sensitivity to tuberculin, and with the warning stressed by Rich (1944) that tuberculin sensitivity may not necessarily run *pari passu* with resistance In the past we have placed too much reliance on single tuberculin tests and radiographs The story of man's resistance to tuberculosis is a serial and it ends only at death Although we cannot measure it by titration in a test-tube, there is sufficient clinical evidence for the belief that his resistance increases with age until the later years of life, when it appears to decline, senile tuberculosis has a prognosis which is little worse than that of the child Man's racial resistance, however, is unevenly distributed It is only the well-salted white races who display this moderately good resistance There are primitive races in Central Africa with a very low immunity and a group such as the negroes and Indians of North America with a good resistance which is intermediate in its effectiveness Cummins (1939) has described the tuberculosis of white races as "modified," of the primitive natives as "natural" and of the intermediate group of races who are in the process of growing up, immunologically speaking, as "larval" Added to these are the peoples of the old civilizations of the East, such as India and China, who resist the tubercle bacillus fairly well in the environment in which they have lived for centuries but who react badly when brought into modern crowded city and factory conditions

Mechanism of resistance

In man the mechanism of resistance is threefold: (a) anatomical and mechanical, (b) cellular, and (c) humoral As examples of the first group may be cited the intact epithelial lining of the respiratory and digestive tract, the secretion activity of their various glands and the mechanical movements of expulsion with which the tracts are endowed Of the cellular defences the

reticulo-endothelial system is probably the most important The humora defences of blood and tissue fluids are much talked about but difficult to demon strate, and are little understood The treatment of tuberculosis might indeec take on a new aspect if we could measure the antibodies in the circulating blooc as we can those of the enteric group of diseases Obviously all these different mechanisms of resistance combine in a general onslaught on the invading bacillus, and their joint effort is most clearly seen in the lymphatic system. The lymphatic glands, especially those of the broncho-mediastinal and mesenteric groups, constitute indeed a most efficient barrier against the dissemination of the micro-organism

It is customary to describe individual resistance as being of two types, natural, which is inherent in each animal species, and acquired, which is developed as the result of the vaccinating effect of a small dose of infection.

Natural resistance

In the lower animals, the most striking feature of the mechanism is phagocytosis, and it is so efficient that it is impossible to infect many of these animals with the tubercle bacillus at all In mammals, resistance is a more differentiated function and results in a series of tissue reactions which vary with each species but which have also fixed characteristics for the species. The exudation of plasma and the migration of macrophages from the reticulo-endothelial system to the site of the injection are common to all To these may be added, in most animals, the formation of reticulin fibres. Although the tissue reaction is most varied, caseation, extensive collagenous fibrosis and calcification are characteristic qualities of the later stages of the reaction in man, but in some of the more resistant mammals, notably the albino rat, these d

in three distinct types of disease

an extensive multiplication of

phages which become literally

which the condition continues for many months without the usual manifestations

This form

e occurs in

tion accom-

panied by wasting and in which death almost invariably follows in a few weeks

dose. (iii) The third types include

f which we recognize 2 extremes

without meningitis, and (2) a very

but with much fibrosis, calcifica-

and complete healing These forms appear to represent an immunity which

in the reactions to bovine and human

results are much the same There are other

The

animals with the exception of the pig, which is susceptible not only to the human and bovine strains but also to the avian strain

There are yet other differences which may be attributed to anatomical distribution of blood—vascular and lymphatic systems which constitute a special tissue resistance. The relative frequency of lesions in the thyroid in the rabbit and their rarity in the guinea-pig, and the difference in types of pulmonary lesion in the two animals, may be cited as examples

Lastly, there are types of tissue resistance which appear to be inherent in the special nature of tissue, for example, the remarkable resistance of the salivary glands to tuberculosis in man Resistance to the tubercle bacillus is indeed a baffling problem.

Acquired resistance

One of the early contributions made by Koch was his description of the primary and reinfection lesions in the guinea-pig, which has become known as Koch's phenomenon. Much water has run under the bridge since Koch wrote this classical description, and many modifications of the phenomenon are now recognized It is not necessary to quote the whole of this historic description Here are salient points as modified by later researches

(i) If a normal guinea-pig is inoculated intracutaneously with a pure culture of tubercle bacilli the wound as a rule closes and in the first few days seemingly heals

(ii) After 10–14 days, however, there appears a firm nodule which soon opens, forming an ulcer that persists until the animal dies

(iii) Quite different is the result if a tuberculous guinea-pig is inoculated intracutaneously (It is best to use animals that have been infected 4–6 weeks previously)

(iv) In such an animal also the wound closes at first, but in this case no nodule is formed

(v) On the next or second day afterwards the area becomes indurated and assumes a dark colour.

(vi) These changes do not remain limited to the inoculation point but spread to involve an area 0·5–1·0 centimetre in diameter

(vii) In succeeding days the altered skin becomes necrotic

(viii) Finally it sloughs, leaving a shallow ulcer which usually heals quickly and permanently

(ix) After the first inoculation bacilli reach regional lymph nodes in 1–4 hours; after the second they take as long as 4 days.

(x) This striking effect is produced not only by living tubercle bacilli but also by dead bacilli

It is quite impossible to [illegible]

allergy has become so debauched by indiscriminate use as to be almost meaningless,

and he sees no connexion between hypersensitivity and specific acquired res *to the bacillus. Acquired resistance can remain intact in his view after* sensitivity has spontaneously declined to the vanishing point. Topley and (1943), however, hold the view that both " experimental and field evidence *that allergy is a step on the road to immunity". Put in the form of a* question the issue in clinical medicine today is—Does the arrested p infection confer immunity ? Most clinicians believe that it does, but the labo worker is unable to measure immunity and he has no *really satisfactory* to give Possibly there are as many answers as there are infected person

In recent years attempts have been made to carry the matter a step f by a chemical analysis of the split products of the tubercle bacillus Thre of fractions have been isolated, proteins, carbohydrates and lipids, the pr being responsible for the hypersensitivity phenomena, the carbohydrate antibody production and the lipids for the formation of tuberculoid tissue so far, except for the use of the protein fraction (P.P.D) as a diagnostic tuber no clinical results have been obtained by their use.

PROPHYLAXIS

... does confer immunity, it is logic ...

B.C.G (bacillus Calmette Guérin) consists of living cultures of bovine tub bacilli which have lost virulence by repeated sub-cultivation on a potato-gly ox bile medium since 1906 to a degree that they have lost their power to c progressive tuberculosis in the guinea pig After 230 sub-cultures the orga has been kept on ordinary media with a transfer to a bile salt medium at e ... to prevent ...

1935).

... strong presumptive case for the value of B C ... ing enough to *justify* ... venting tuberculosis.

Of the numerous investigations reported on the vaccination of infants ...

children of tuberculous parents Wallgren (1934 and 19...) ... infant that was considered by the Gothenburg dispensary to be in dange ... from contact The infantile tuberculosis death rate fell from 3 9 ...

At Chicago Rosenthal, Blahd and Leslie (1945) vaccinated by ... puncture method the child of every alternate mother who had consented at Cook Country Hospital and reported the following results.

TABLE XIV

B C G VACCINATION OF INFANTS IN CHICAGO

Group	Sub-group	No of Children	No of cases of tuberculosis	No of deaths from tuberculosis
Non-contact	Vaccinated	1,204	3	1
	Control	1,213	23	4
Contact	Vaccinated	98	1	0
	Control	63	4	3
Contact and non-contact together	Vaccinated	1,302	4	1
	Control	1,276	27	7

In New York City, a similar infantile investigation was carried out with illuminating results (Levine and Sackett, 1946), since it is demonstrated what an important part selection plays in the result obtained.

TABLE XV

B C G VACCINATION OF INFANTS IN NEW YORK CITY

Period	Alternative selection	Vaccinated group			Control group		
		No of children	No of deaths from tuberculosis	Tuberculosis mortality, per cent	No of children	No of deaths from tuberculosis	Tuberculosis mortality, per cent
1926–32	No	445	3	0 67	545	18	3 30
1933–44	Yes	566	8	1·41	528	8	1 52

To compare with these figures, Heimbeck (1948) gives results as follows for the vaccination of the general population of Oslo.

TABLE XVI

B C G VACCINATION IN OSLO

	No of cases	Observation years	Tuberculosis		Rate per 1,000 observation years	
			Disease	Deaths	Morbidity	Mortality
Von Pirquet +	2,421	19,701	54	6	2 7	0 3
Von Pirquet —	2,833	20,112	182	13	9 1	0 6
B C G vaccinated	566	4,158	8	0	1 9	0
Von Pirquet — (Contacts)	523	2,833	44	7	15 5	2 5

Malmros (1948) records the results of the vaccination of 22,413 persons, including 8,040 new-born infants, 7,836 children over 1 year of age and 6,537 adults and showed that over 94 per cent became tuberculosis positive within 6 weeks of the inoculation and that only one has subsequently developed pulmonary tuberculosis —and that a pleurisy in a probationer nurse who was tuberculin negative in spite of two B C G vaccinations Hyge (1947) reports an interesting incident in which an epidemic of tuberculosis caused by a female teacher broke out in a girls' school when the incidence of disease was as shown in Table XVII.

TABLE XVII

INCIDENCE OF TUBERCULOSIS IN GIRLS' SCHOOL

Tuberculin reaction	No of pupils	B C G	Incidence of pulmonary tuberculosis	Deaths
Tuberculin +	105		2	—
Tuberculin —	200	106 vaccinated	2	—
		94 unvaccinated	41	1

These groups of figures may be criticized in that the methods of Levine and Sackett *were not satisfactory in the selection of controls, while Rosenthal and his* colleagues and Heimbeck afford incomplete information in several particulars.

The main investigations on B.C G. vaccination of nurses are those of Ferguson (1946) in Canada, and Heimbeck (1948) in Norway Ferguson included no control group and merely judged the efficacy of the B C.G. vaccination by a diminution in morbidity compared with the previous five-year period. Heimbeck's work in Norway is generally considered to provide the surest backing for B C.G. as a prophylactic. He, however, transferred in his analysis the medically Von Pirquet-negative nurses to the positive group within one year of their primary infection.

TABLE XVIII

RATES OF TUBERCULOUS DISEASE AMONG ULLEVAL NURSES, 1924-46

	No of nurses	Observation years	Tuberculosis		Rate per 1,000 observation years	
			Disease	Deaths	Morbidity	Mortality
Pupil nurses in training—						
Von Pirquet +	668	1,772	22	—	12 4	—
B C.G	*501*	*1,450*	*35*	3	*24 1*	2 1
Von Pirquet — re	284	687	97	10	141 2	14 6
Graduate nurses—						
Von Pirquet + re	504	4,792	13	1	2 7	0 2
B C G.	377	3,318	7	2	2 1	0 6
Von Pirquet — re	178	1,610	8	2	5 0	1 2

Finally Aronson and Palmer (1946) started a carefully controlled study among North American Indian children in 1935 The subjects aged between *1* and *20* years were tuberculin tested with P.P D and those who failed to react to 0 0005 milligram were divided into 2 groups, those of one group were injected intra- [illegible]

in white peoples possessing a higher degree of basic immunity.

TABLE XIX

B C G VACCINATION OF NORTH AMERICAN INDIAN CHILDREN AND YOUNG ADULTS

Group	No of subjects	No developing non-pulmonary tuberculosis	No developing pulmonary tuberculosis	T B case rate per *1,000 persons* —years	No of deaths *from all* causes	No of deaths *from* tuberculosis
Vaccinated	1,550	9	8	2 0	34	4
Non-vaccinated	1,457	48	20	9 0	60	28

Such then is the evidence on which the case for the use of B C G. vaccination as a prophylactic in tuberculosis is based, and while the evidence is suggestive, the impartial judge must conclude that it is not proven It is probable that the careful medical supervision which a B C G vaccination scheme necessitates could by itself eradicate tuberculosis from the community in a generation

BIBLIOGRAPHY

Aronson, J D, and Palmer, C E (1946) "Experience with B C G Vaccine in Control of Tuberculosis among North Americans" *Publ Hlth Rep Wash*, 61, 802

Bashford, H H, and Scott, W L (1936) "Pulmonary Tuberculosis in Industry Incidence and after-history an analysis of 3,755 cases" *Lancet*, 1936, 2, 1115

Blacklock, J W S (1932) "Tuberculous Disease in Children" *Spec Rep Ser Med Res Coun Lond* No 172 London, H M Stationery Office

Bradbury, F C S (1933) *Causal Factors in Tuberculosis* London, National Association for Prevention of Tuberculosis

— (1947) "The Lancashire Mass Radiography Unit" *Med Offr*, 77, 153

Brieger, E M (1944) *Papworth's Families* London, Heinemann

Brooks, W D W (1944) "Management of Minimal Pulmonary Tuberculosis Disclosed by Fluorography" *Lancet*, 1, 745

Brownlee, J (1918) "An Investigation into the Epidemiology of Phthisis in Great Britain and Ireland" *Spec Rep Ser med Res Coun Lond*, No 18 London, H M Stationery Office

Bushnell, G E (1921) *A Study in the Epidemiology of Tuberculosis* London, Bale

Calmette, A (1928) "La premunition ou vaccine preventive des nouveau-nés contre la tuberculose par le B C G" *Ann Inst Pasteur*, 42, 1

Carmalt Jones, D W (1933) "Inquiry into Incidence of Tuberculosis Nurses in New Zealand Hospital" *Tubercle, Lond*, 15, 59

Chaussé, P (1916) "Nouvelles recherches sur la contagion de la tuberculose par l'air expiré pendant la toux" *Ann Inst Pasteur*, 30, 613

Cheeseman, E A (1941) "Comparison between Direct and Indirect Occupational Risk in Mortality from Pulmonary Tuberculosis" *J hyg, Camb*, 41, 463

Clark, K C, Hart, P D'Arcy, Kerley, P, and Thompson, B C (1945) "Mass Miniature Radiography of Civilians" *Spec Rep Ser Med Res Coun, Lond* No 251 London, H M Stationery Office

Clive, F T (1943) 'Mass Radiography in Women review of 30,000 examinations in W A A F. recruits" *Tubercle, Lond*, 24, 63

Cobbett, L (1917) *Causes of Tuberculosis* London, Cambridge University Press

Collis, E L (1923) 'Influence of Industrialism upon Age Incidence of Phthisis' *Tubercle, Lond*, 4, 241

— (1922) 'Mortality of Coal Miners" *J indust Hyg* 4, 256

Cox G L, *et al* (1929) "Fate of Young Children in Tuberculous Households" *Tubercle, Lond*, 10, 497

— Heaf, F R G, McDougall, J B, and Powell, D A (1942) *Infection and Environment in Tuberculosis* Maidstone, British Legion, Preston Hall

Cummins, S L (1939) *Primitive Tuberculosis* London, Bale

Daniels, M (1944) "Primary Tuberculous Infection in Nurses" *Lancet* 2, 165, 201 244

— Ridenhalgh, F R, Springett, V H, and Hall, I M (1948) *Tuberculosis in Young Adults (Prophit Tuberculosis Survey, 1933–1944)* London, Lewis

Dow, Dorothy J, and Lloyd, W E (1931) "The Incidence of Tuberculous Infection and its Relation to Contagion in Children under 15 an analysis of 1,220 children from the Brompton Hospital Research Department" *Brit med J*, 2, 183

Evans, A. G (1943) "Incidence of Pulmonary Tuberculosis of Adult Type in the R.A F results of mass radiography of 75,000 cases" *Brit med J*, 1, 565

Ferguson, R G (1946) "B C G Vaccination in Hospitals and Sanatoria in Saskatchewan. study carried out by the National Res. Council of Canada." *Canad J. publ Hlth*, **37**, 435

Gloyne, S. R. (1946). "The Relationship Between Primary and Adult Pulmonary Tuberculosis" *Brit J. Tuberc*, **40**, 93

— (1944). *Social Aspects of Tuberculosis*. London, Faber and Faber.

Griffith, A. S (1937). "Bovine Tuberculosis in Man" *Tubercle, Lond*, **18**, 529.

Hart, P D'Arcy (1932) "The Value of Tuberculin Tests in Man" *Spec Rep. Ser. med Res Coun Lond*, No 164. London, H M Stationery Office.

— and Wright, G P (1939) *Tuberculosis and Social Conditions in England.* London; National Association for Prevention of Tuberculosis

Heaf, F R. G (1947) "B C G Vaccination Against Tuberculosis" *Month. Bull. Min Hlth Publ. Hlth Serv*, **6**, 184

— and Rusby, N L (1948) *Recent Advances in Respiratory Tuberculosis*, 4th ed. London; Churchill.

Heimbeck, J (1938) "Incidence of Tuberculosis in Young Adult Women, with Special Reference to Employment" *Brit J Tuberc*, **32**, 154.

Hill, A B (1929) "An Investigation into the Sickness Experience of Printers (with special reference to the incidence of tuberculosis)" *Med Res Coun Industr Fatigue Board, Report No 54.* London, H M Stationery Office

Hyge, T. V. (1947) "Epidemic of Tuberculosis in State Schools with Observation Period of about 3 Years" *Acta tuberc, Scand*, **21**, 1

Inkster, J., and Gloyne, S R (1921) The Bactericidal Action of Gastric Juice on *B Tuberculosis*" *Brit med. J*, **2**, 1024

Jacobs, A L (1948) "Prophit Survey. analytical review." *Tubercle, Lond*, **29**, 201.

Jameson, W (1946) *The State of the Public Health during Six Years of War.* London; H M Stationery Office

Kayne, G G. (... London; Milford

Lange, B (192 ... e infektion mit Tuberkelbaciller

— (1931) ... von Infektions dosis, ... Immunität für Entstehung und Verlauf der Tuber-

... B C.G Immunization in New York

... "A Reinvestigation of Children ... d J, **1**, 818

... " *Brit med J*, **1**, 1129

... usheitung der Tuberculose" *Virchow's Arch*, 100, 420

... with

Opie, E L, McPhe ... Tuberculosis ... *Zeit*

Redeker, F. (1937) ... 1937, 79 42

... *land and Wales for the Year 1945.* London;

... 60 1

... ophit

Rosenthal, S R, Bland, M, and ... 5) "Ten Years' Experience with *B C G*, Experimental and Clinical" *J Pediatrics*, **26**, 470

Scott, H H (1930) "Tuberculosis in Man and Animals" *Spec. Rep Ser med Res. Coun*, No 149 London, H M Stationery Office

Sigurdsson, J (1945). *Studies on the Risk of Infection with Bovine Tuberculosis to the Rural Population with Special Reference to Pulmonary Tuberculosis* Trans by Hans Anderson London, Oxford University Press

Smith, C M (1947) "Northamptonshire—Mass Miniature Radiography, 1945–46." *Med Offr*, 77, 109

Springett, V. H (1950) "A Comparative Study of Tuberculosis Mortality Rates" *J Hyg, Camb*, 48, 361

Stewart, Alice, and Hughes, J P. W (1951) "Mass Radiography Findings in the Northamptonshire Boot and Shoe Industry, 1945–6" *Brit med J*, 1, 899.

— — (1949) "Tuberculosis in Industry: an epidemiological study." *Brit med. J.*, 1, 926

Stocks, P (1949) "A Study of Tuberculosis Mortality in England and Wales" *Tubercle, Lond*, 30, 50

Todd, T R R (1926) "Post-mortem Tuberculous Lesions" *Edinb med J*, 33, 219, 303

Topley, W. C C., and Wilson, G S (1943) *Principles of Bacteriology and Immunology* London; Arnold.

Traill, R R (1942) "Early Diagnosis of Pulmonary Tuberculosis" *Lancet*, 2, 413.

Ustevdt, H C (1942) *Pulmonary Tuberculosis* Trans by A. L Jacobs London, Bale

Wallgren, A (1934) "Value of Calmette Vaccination in Prevention of Tuberculosis in Children" *J Amer med Ass*, 103, 1341

— (1948) "B C G Vaccination, is it of any value in control of tuberculosis?" *Brit med J*, 1, 1126.

Wayburn, E (1946) "Mass Miniature Radiography survey in United States Army Air Forces" *Amer Rev Tuberc*, 54, 527

Wells, A Q (1946) "The Murine Type of Tubercle Bacillus" *Spec. Rep Ser. med Res Coun.* No 259 London, H M Stationery Office

Wilson, G S (1947). "The Value of B C.G Vaccination in Control of Tuberculosis" *Brit. med J*, 2, 855

Wingfield, M C, and Macpherson, A Margaret (1936) "Latent Adolescent Pulmonary Tuberculosis" *Brit med J*, 1, 741.

Woods, Hilda M, and Russell, W T (1936) *An Introduction to Medical Statistics*, 2nd ed London, Staples

CHAPTER 11

PULMONARY TUBERCULOSIS IN CHILDHOOD

A MARGARET MACPHERSON

INCIDENCE

TUBERCULOUS pulmonary lesions in children are of frequent occurrence although not necessarily of pathological significance Reports of surveys on tuberculin testing in England and Wales, *between 1930 and 1949, show that between 54 and 70 per* cent of children in towns are infected by tubercle bacilli by the age of 16 years and a rather lower percentage in country districts (Hart, 1929; Schlesinger and Hart, *1930*, Lloyd and Dow, *1931*; Prophit Tuberculosis Survey, *1948*; Crowe, 1942). Since the greater number of these are infected by inhaling the organism, it follows that an active tuberculous pulmonary lesion is present in a large number of children during childhood. For the most part, these lesions are of little clinical significance since the majority both come into existence and heal without detection In some cases, however, the lesions *do not follow the expected course of resolution* and healing, but give rise to complications which are of clinical importance. The primary infection then is associated with definite disease, which may vary in degree *from slight malaise to severe illness which may be dramatic and fatal*

Tuberculin tests

A positive reaction to the tuberculin test indicates that primary infection has taken place, the skin becoming hypersensitive to tuberculin once tubercle bacilli have entered the body Hypersensitivity develops usually within a period up to 8 weeks from the time that infection takes place, and it persists, with *certain* [illegible] and as a rule for the duration of a life-time In certain [illegible] nce, during [illegible] ne terminal [illegible] of America [illegible] the [illegible] ster [illegible] his [illegible] *has not been confirmed in Great Britain*

The methods most commonly used for tuberculin testing at the present time are (1) the von Pirquet, (2) the Mantoux and (3) the percutaneous tests.

The von Pirquet test

The von Pirquet test is carried out on the anterior surface of the forearm The skin is cleansed, after which a drop of *Old Tuberculin (O T.) is placed on the skin,* which is then scarified through the drop by means of a needle or scalpel. The tuberculin is allowed to dry, no covering being applied, and the reaction is read in 48 hours A positive reaction shows redness and induration at *the site, any in-*duration of 5 millimetres or more in diameter being taken as a positive result.

The Mantoux test

For the Mantoux test, an intradermal injection is made in the forearm, using 0·1 millilitre of diluted Old Tuberculin containing either 0·01 milligram (1 : 10,000 dilution), 0·1 milligram (1 : 1,000 dilution) or 1·0 milligram (1 : 100 dilution) If the presence of an active tuberculous lesion is suspected it is usual to make the first test with 1 : 10,000 dilution but, during routine testing, in order to avoid having three tests, some doctors prefer to begin with 1 : 1,000 dilution. If the reaction to this is negative, 0·1 millilitre of 1 : 100 dilution (1 milligram) is injected A negative result, when 1 milligram of Old Tuberculin is used, is, for practical purposes, evidence in children that infection has not taken place

As with the von Pirquet test, the Mantoux test is read after 48 hours, and a positive reaction is one giving erythema and induration, the latter measuring 5 millimetres or more. Instead of diluted Old Tuberculin, purified protein derivative (P P D) may be used for the Mantoux test , this is a substance which is purer in tuberculoproteins than O T and which is less likely than is O T to produce pseudo-reactions when used in the stronger solutions P P D is used in two strengths, 0·1 millilitre of a dilution containing 0·00002 milligram being given first, followed, if the reaction is negative, by 0·1 millilitre containing 0·005 milligram

Percutaneous tests

Percutaneous tests have the obvious advantage for children of not requiring scarification or injection and they are now used extensively for the routine testing of children Moro's ointment and Danish ointment have been in use for some years, but more recently tuberculin jelly has largely taken their place The skin, usually over the sternum or between the scapulae, is cleansed with ether or acetone to remove fatty substances The tuberculin jelly or ointment is applied and covered with adhesive plaster This is removed after 48 hours and the tests are read after a further 12 hours If the jelly is applied in the form of a " V ", it is easier to read slight reactions Erythema, papules or vesicles in the area covered by the jelly indicate a positive reaction The test is more sensitive, especially in older children, if, before applying the jelly, the skin is stroked gently with fine abrasive paper known in the trade as flour paper (Dick, 1950)

Comparisons and standardization

Comparisons between the sensitivity of these tests show that the von Pirquet is roughly equivalent to the Mantoux test with 1 : 1,000 O T , and that the jelly test is slightly more sensitive than this but less sensitive than a Mantoux test with 1 : 100 O T (Deane, 1946) Of the materials used for intradermal injections, P P D , first strength (0·00002 milligram) is equivalent to 1 : 10,000 O T

It has been suggested that an international nomenclature for materials for tuberculin testing should be used, and it is recommended by the World Health Organization that 0·01 milligram of O T should be the unit of International Standard for Old Tuberculin

PRIMARY PULMONARY LESION

Situation

The characteristic pulmonary lesion is situated near the periphery of the lung in

: sub-pleural region. It is usually single but may be multiple. Ghon (1916) ınd that out of 170 cases, 123 showed single foci, and Blacklock (1932) found 125 ;es with single lesions out of a total of 148 cases. According to published records, : lesions are present more often on the right side than the left; they occur most quently in the right upper lobe, and least often in the right middle lobe (Ghon, 16; Blacklock, 1932).

thology and course of typical lesion

Histological evidence of early changes in primary lesions is not easily obtained d has only been available when found by chance in autopsies on children dying m other causes than tuberculosis. Experiments on animals have provided ther evidence and helped to build up the picture.

e primary reaction

The first reaction of the lungs appears to be a non-specific one such as is produced any foreign body. The number of tubercle bacilli in the lesion increases, and a cific reaction of the tissues follows with *tubercle formation, necrosis and case-on.* The size of the lesion varies. Blacklock (1932) found that the average size children in Glasgow was that of a hazel nut; Ghon (1916) reports the majority be the size of a pea but that they varied from the size of a millet seed to that of a lnut. Fibrous tissue develops, forming a capsule round the lesion and dividing it m healthy lung tissue. This is a significant finding, and the encapsulation is ially more complete in primary lesions in children than in those found in young ılts. Even in children, however, the lesion is not always confined inside the sule, for a few tubercles may be found outside, the infection having probably ended along lymph ducts. The stage of reaction is followed by healing, and the ın lesion, as well as the scattered tubercles, is largely replaced by fibrous tissue h, in many cases, deposition of calcium. The smaller fibrous scars may be im-ssible to detect and it is only the larger ones, or those which contain calcium, that be found histologically. At a later date some lesions may undergo further inges and become ossified. Although these lesions are apparently healed, it has n shown that some contain living tubercle bacilli. The time taken for these inges to take place varies in different circumstances, depending on the general ıdition of the child and on its environment.

ındular involvement

At the same time that the early changes are developing in the pulmonary lesion lymphatic glands become infected. Tuberculous changes are found in the *ncho-pulmonary glands corresponding* to the site of the pulmonary lesion, also the tracheo-bronchial glands. In some cases the paratracheal glands and those the carina are infected, and, when the infection is a heavy one, there may be a ead of infection to the glands of the opposite side, so that, for example, a primary monary lesion on the right side may be associated with lesions in the left cheo-bronchial glands as well as in those of the right side.

As in the pulmonary lesions, large numbers of tubercle bacilli are found in the nds at an early stage. Caseation is usually more marked in the glandular tissue n in the pulmonary lesion. This is specially so in young children, in whom a all pulmonary lesion is often associated with large caseating gland masses.

Healing takes place normally in the glands by resolution and the disappearance of caseous material often with deposition of calcium. The two associated lesions in the lung parenchyma and in the lymphatic gland are referred to as the primary complex. The names of the first authors to draw attention to these lesions—Parrot (1876) and Ghon (1916)—are often applied to the foci or nodes.

Radiological evidence

In cases with the typical primary lesion, there are no clinical manifestations of the condition. Radiological examination may or may not give any evidence; the early stage of a small primary lesion may not be visible in the radiograph, although enlarged hilar glands are more likely to be seen. When calcium is present in the lesion, it is then possible to detect its presence and in the later healing stage, there may be definite radiological evidence of a primary complex, which in the early stage it was not possible to see (*see* Figs 105 and 106).

Primary lesions producing clinical manifestations

The children who become ill as a result of tuberculous infection are those in whom the primary lesion has not followed the benign course described above. In these cases the primary lesion has given rise to certain complications which produce a morbid condition. The complications may be considered under fo headings

(1) Pulmonary lesions which do not become circumscribed but either (a) develo into large spreading areas of tuberculous broncho-pneumonia or (b) develop by gradua spread into lesions typical of adult disease.

(2) Gross infection of lymphatic glands, which causes occlusion of the lumen of a bronchus, either by ulceration through the wall or by pressure and distortion.

(3) Large pleural effusions.

(4) Blood-stream infection from the pulmonary or lymphatic lesions.

The occurrence of these complications cannot be predicted, but certain circumstances make them more probable. When primary infection takes place during infancy, it is more often associated with clinical illness than when it occurs between the ages of 5 and 12 years. Close contact with heavily infected persons, providing the possibility of massive infection or of repeated infections, appears to be directly associated with the appearance of large spreading pulmonary lesions and with gross glandular involvement. There is evidence that lowered resistance also plays a part in the development of the progressive lesions and influences the extent of glandular lesions. Resistance may be lowered as the result of general undernourishment or of intercurrent infections, measles and whooping cough are not infrequently associated with active tuberculous lesions. Inherited lack of immunity in certain races or families is another probable factor.

The clinical conditions associated with the four kinds of complications referred to have certain features in common. The extent of the clinical and radiological findings does not necessarily coincide with the severity of the illness: some children are acutely ill, while others suffer from little more than slight malaise, although both types of case may show signs of extensive pulmonary or glandular lesions. With the exception of some cases of pleural effusion, the illness is of several weeks' or months' duration. If it is not fatal, the tuberculous process in younger children may heal, leaving no evidence of residual tuberculous activity

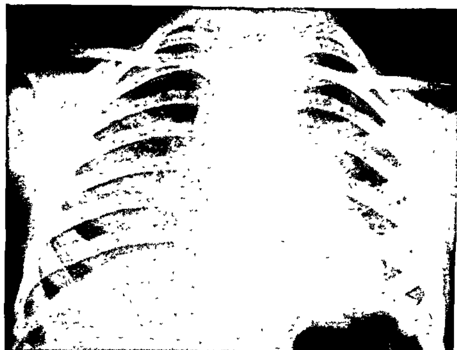


FIG 105 —Patient G F, aged 2 years, showing primary tuberculous lesion, 7 7 36, enlarged hilar shadow on left side with no obvious pulmonary lesion

Although the tuberculous lesion heals, new non-tuberculous lesions may develop, as the result of damage sustained by the lung or other structures at the time of the original active tuberculous lesions, and these non-tuberculous lesions may give rise to more permanent symptoms and illness The spectacular and devastating effects of tuberculous infection in children make a deep impression, but almost equally impressive is the capacity which a child, who does not succumb to infection, has for overcoming—and overcoming completely—large caseating tuberculous lesions in the lung or the lymphatic tissues

Tuberculous broncho-pneumonia

The primary lesion may not remain localized, and may develop into an area of broncho-pneumonia with large caseating areas and areas of more acute necrosis. Tuberculous broncho-pneumonia may also follow erosion into the bronchial lumen of tuberculous material from an adjacent lymphatic gland, the material being aspirated into the segment of lung beyond

Acute cases

Tuberculous broncho-pneumonia may give rise either to an acute illness or else to a subacute condition with only slight malaise When the illness is acute, there is a high, irregularly swinging temperature and the child is listless and without appetite The physical signs and clinical picture at first resemble those of broncho-

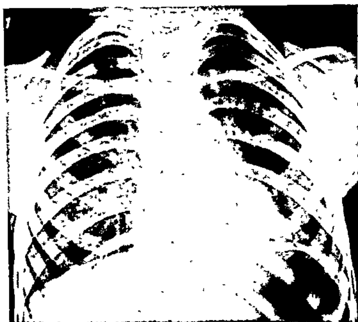


FIG 106 —Same patient as shown in Fig 129, 4 7 39 the calcified pulmonary lesion is seen in left upper lobe with calcium in left hilar glands

pneumonia due to other organisms The possibility that the condition is tuberculous should be considered when there is no response to treatment with sulpha drugs and penicillin, and when there is no evident resolution of the pneumonia over a period of weeks These features, associated with wasting, a history of household contact, and the positive result of a Mantoux test (using 1 . 10,000 O T. or 1 · 1,000 O T.) in a child under 3 years of age, are further aids to the correct diagnosis, which may in some cases be confirmed by finding tubercle bacilli, either by direct examination or by culture from stomach washings, or in the sputum if this can be obtained

The radiological appearance of the condition is illustrated in Fig 107. There are irregular, patchy, mottled areas, which later may show evidence of breaking down with cavity formation It is not uncommon to find associated pleural effusion or collapse of part of the lung, resulting from lesions in the hilar glands (Fig 108)

Subacute cases

In the subacute cases there is little constitutional disturbance, although there are usually slight irregular pyrexia occurring at intervals and a failure to gain weight. Physical signs and radiographs show evidence, however, of extensive broncho-pneumonic lesions, which remain little changed for many weeks or months



FIG 105 —Patient G F, aged 2 years, showing primary tuberculous lesion, 7.7.36, enlarged hilar shadow on left side with no obvious pulmonary lesion.

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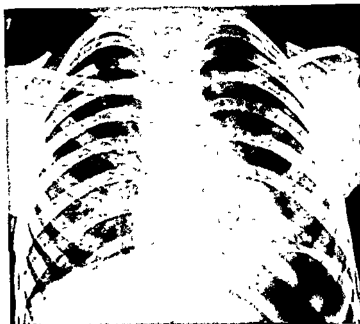


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Although the tuberculous lesion heals, new non-tuberculous lesions may develop, as the result of damage sustained by the lung or other structures at the time of the original active tuberculous lesions, and these non-tuberculous lesions may give rise to more permanent symptoms and illness The spectacular and devastating effects of tuberculous infection in children make a deep impression, but almost equally impressive is the capacity which a child, who does not succumb to infection, has for overcoming—and overcoming completely—large caseating tuberculous lesions in the lung or the lymphatic tissues

Tuberculous broncho-pneumonia

The primary lesion may not remain localized, and may develop into an area of broncho-pneumonia with large caseating areas and areas of more acute necrosis. Tuberculous broncho-pneumonia may also follow erosion into the bronchial lumen of tuberculous material from an adjacent lymphatic gland, the material being aspirated into the segment of lung beyond

Acute cases

Tuberculous broncho-pneumonia may give rise either to an acute illness or else to a subacute condition with only slight malaise When the illness is acute, there is a high, irregularly swinging temperature and the child is listless and without appetite. The physical signs and clinical picture at first resemble those of broncho-

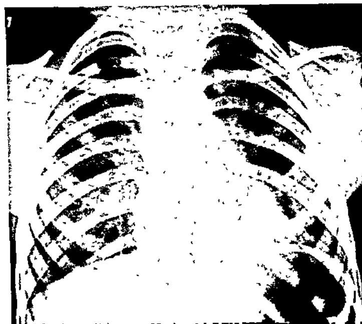


FIG 106—Same patient as shown in Fig 129, 4 7 39 the calcified pulmonary lesion is seen in left upper lobe with calcium in left hilar glands

pneumonia due to other organisms The possibility that the condition is tuberculous should be considered when there is no response to treatment with sulpha drugs and penicillin, and when there is no evident resolution of the pneumonia over a period of weeks These features, associated with wasting, a history of household contact, and the positive result of a Mantoux test (using 1 10,000 O T. or 1 1,000 O T) in a child under 3 years of age, are further aids to the correct diagnosis, which may in some cases be confirmed by finding tubercle bacilli, either by direct examination or by culture from stomach washings, or in the sputum if this can be obtained

The radiological appearance of the condition is illustrated in Fig 107. There are irregular, patchy, mottled areas, which later may show evidence of breaking down with cavity formation It is not uncommon to find associated pleural effusion or collapse of part of the lung, resulting from lesions in the hilar glands (Fig 108)

Subacute cases

In the subacute cases there is little constitutional disturbance, although there are usually slight irregular pyrexia occurring at intervals and a failure to gain weight. Physical signs and radiographs show evidence, however, of extensive broncho-pneumonic lesions, which remain little changed for many weeks or months



FIG 107.—Patient R.W., showing acute tuberculous broncho-pneumonia from which the child died several weeks later

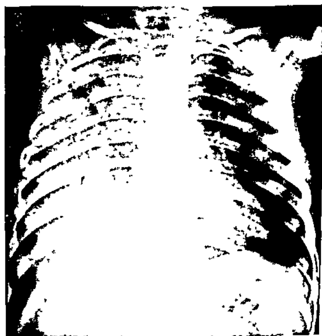
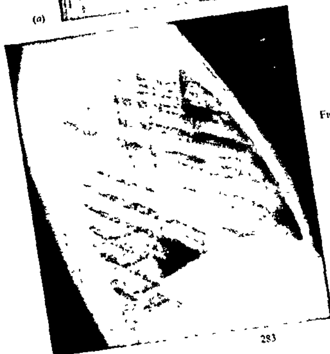


FIG 108—Patient T L, aged 1 year 9 months Primary tuberculous lesion complicated by pleural effusion and broncho-pneumonia, the child died 6 weeks later

(a)



(b)

Fig. 109.—Patient D.C. aged 2 years 4 months. (a) 10.7.46 subacute broncho-pneumonia. (b) 16.3.51 complete clinical recovery with calcification of earlier lesions.



FIG 107.—Patient R W., showing acute tuberculous broncho-pneumonia from which the child died several weeks later

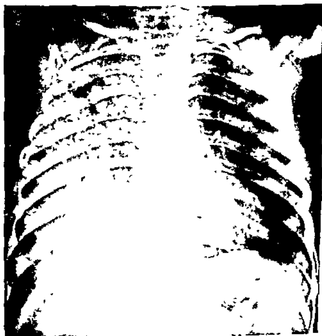


FIG. 108—Patient T L, aged 1 year 9 months Primary tuberculous lesion complicated by pleural effusion and broncho-pneumonia, the child died 6 weeks later



(a)



(b)

FIG 109—Patient D C, aged 2 years 4 months; (a) 10 7 46, subacute bronchopneumonia, (b) 16 3 51, complete clinical recovery with calcification of earlier lesions

Eventually the condition clears and the child is left with no residual sign or with calcified scars (Fig 109).

Miliary tuberculosis of the lung

Miliary lesions of the lung may appear as part of a generalized infection and be accompanied by acute illness Diagnosis of the condition is dependent on radiological examination Since streptomycin has been available for these cases, the

ns may also be seen in the
:hronic or subacute lesions
vidence, or there may be

Tuberculous infiltration of adult type

In the older age-groups of children, primary lesions may quickly develop into spreading infiltrating lesions, such as are found in young adults The course, prognosis and treatment are similar to those of the tuberculosis of young adult life

Complications due to gross hilar adenitis

Pathogenesis

Complications following gross tuberculous lesions in the thoracic lymph-glands are more likely to occur than are complications resulting from the pulmonary lesion The large caseating glandular masses, immediately adjacent to and lying in the angle between the main bronchi and their branches, may cause distortion of the bronchi, with diminution in the size of the lumen and alteration in the direction of the bronchi, or, by pressure, may cause narrowing in the bronchial lumen Tuberculous lesions may also ulcerate through the bronchial wall, causing congestion of mucous membranes or an extension of tuberculous processes into the wall of the bronchi, or the tuberculous glandular tissue may rupture into a bronchus.

Occlusion of the lumen will result in collapse of the lung segment or lobe beyond the bronchus. This is a not uncommon complication of primary tuberculosis Which lobe or segment of the lung is involved depends on the extent of the glandular lesion, and not entirely on the position of the primary lesion. It is quite usual to find the primary pulmonary lesion in a part of the lung other than that which is collapsed, and it is not uncommon, when more than one lobe of the lung is collapsed, to find that both lungs are involved. In many cases the lung re-expands when the block in the lumen clears, and the lung regains its normal clinical and radiographic appearance The clearing of the bronchial lumen is necessarily a slow process when ulceration has taken place through the wall of a bronchus, and re-expansion may not take place for 1–2 years. In a recent investigation of such cases, it was found that, out of 28 cases of collapse associated with recent primary lesions, 26 had re-expanded within a period of 3 years (Macpherson and Lutwyche, 1950)

In a small proportion of cases, the lung tissue does not re-expand although the bronchial lumen becomes patent, and of this small number some eventually develop bronchiectasis. It is not clear from our present knowledge of this subject what are the determining factors for the persistence of collapse, but there is little doubt that the presence of intercurrent infection in the bronchi is one important factor. When this is present there is a greater liability for bronchiectatic changes to occur.

Erosion of tuberculous material from glands into the bronchus, when it does not block the bronchus, may result in bronchogenic spread of infection into the lung beyond, giving rise to tuberculous broncho-pneumonia. Such a case, seen at Guy's Hospital, was described in detail by Brock, Cann and Dickinson (1937)

Clinical picture

Symptoms associated with large masses of caseating glands are often indefinite and may be easily overlooked, even in those cases in which there is also pulmonary collapse There are usually some malaise, lack of normal gain in weight and occasional pyrexia. The pyrexia is irregular, occurring over a period of 3 or 4 days, when it rises to between 100° and 101° F., followed by several days with no abnormal rise. This type of record is more usual than a regular evening rise of temperature

Pressure on a bronchus gives rise to certain characteristic symptoms , there is often present a wheeze, which is most obvious during exertion, and there may be a spasmodic cough resembling that of whooping-cough Apart from these there are few localizing symptoms On examination of the chest, signs of collapse of a part of a lung may be present, but even if one entire lobe is collapsed, there is not necessarily any displacement of the mediastinum or heart Emphysema of the remaining lobes of that lung compensates for the collapse, and presumably the large mass of glands, which is to some extent fixed to surrounding structures, tends to immobilize the mediastinum Radiological examination will confirm the diagnosis of collapse It is important (especially when the middle lobe is involved) that a lateral radiograph be taken, because, in the postero-anterior position, the condition is not always obvious Tomograms may be valuable to show narrowing of the bronchial lumen

Broncho-pneumonic lesions occurring after the aspiration of infected material will give rise to the symptoms and signs described above The following case, typical of many primary lesions, will serve to illustrate some of the points to which reference is made

D S , a boy aged 1 year, was brought for examination on 9.12 36 He was a contact of his mother, who had had a haemoptysis and a positive sputum when the child was 4 months old. Between the ages of 6 and 8 months there was no contact with the mother, who went to a sanatorium After her return she had had no positive reactions to sputum tests The child was breast-fed until the mother's condition was diagnosed When seen the child was well and had a normal radiograph, and the Mantoux test with O T. 1 100 was negative He was seen again on 23 1 37 and 3 4 37, when radiographs were normal and the Mantoux test was still negative to O T 1 100 On 3 7 37, 3 months later, the tuberculin test was strongly positive and the radiograph showed enlargement of the right hilar shadow There were no symptoms Five months later there was radiographic evidence of collapse of the right middle lobe, which had not been apparent in previous films (*see* Fig 110) Three months later, 5 3 38—that is 8–11 months after the primary [illegible]

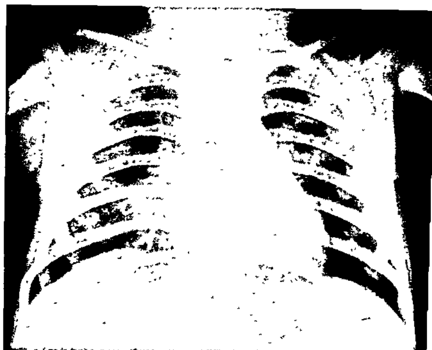


FIG 110 —Patient D S , aged 1 year 6 months, 3 7 37 Primary lesion with collapse of right middle lobe

In November 1938, 1 year and 4–7 months after the first infection, the radiograph showed no evident collapse of the right middle lobe, and commencing calcification was seen at the right hilum and in the right lower lobe From the time of the primary infection up to this date, the child was apparently well and had had no symptoms, apart from the cough referred to above , but during 9 months there had only been 2 pounds' gain in weight Subsequent to this date, when regression of the lesion was evident, there was steady and normal gain in weight

In August 1939, the bronchogram was repeated, and it confirmed re-expansion of the middle lobe (see Fig. 112 (a) and (b)) Calcified deposits increased in the right lower lobe and hilum until February 1940 (2 years and 7–10 months after primary infection), after which time the radiographic appearances remained unchanged. In September 1950, when the boy was 14 years and 10 months old, the appearances remained unchanged (Fig 113)

This case emphasizes certain special points A child runs a definite risk when living in close proximity to a person who is ill with pulmonary tuberculosis, even
... No definite symptoms,
... re present, although
... The time relations
between the events during the course of a primary lesion are of special interest ; the time taken between infection and the development of the maximal lesion was 5–8 months , the period between infection and the onset of definite symptoms was


(a)


(b)

FIG 111 —Patient D S , 1 4 38 Bronchograms showing block of right middle lobe bronchus



(a)



(b)

FIG 112—Patient D S, 17 8 39 Re-expansion of middle lobe, (a) showing also calcification of primary complex

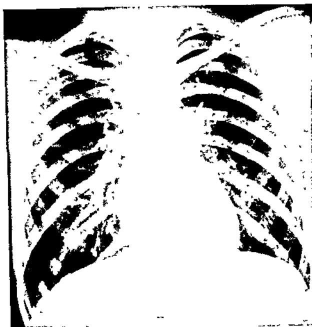


FIG 113—Patient D S, 4 9 50 Calcified primary lesion in right lower lobe and at right hilum

8–11 months, there was re-expansion of the collapsed lobe 1 year after the onset of collapse, healing of the lesion, as judged by the radiographic appearances, had taken place 2½ years after the primary infection

This case also illustrates the fact that the primary pulmonary lesion may not be obvious in the early stages, and may be found at a later date elsewhere than in the collapsed lobe, the latter being determined by the distribution of the lesions in the lymphglands

Pleural effusion

It is not uncommon to find small areas of pleural involvement with localized effusion in the region of the primary pulmonary lesion These are not of any clinical interest and require no special treatment When large pleural effusions occur, they may be difficult to differentiate from those due to other causes The child is usually not acutely ill, and there may be little else than slight pain in the chest to bring the child under medical care The tuberculous nature of the effusion may be suspected when there is a recent history of contact with an open case of tuberculosis, and if the reaction to the tuberculin test is strongly positive in a young child Confirmation may not be possible until the results of culture and guinea-pig inoculation of the fluid are available The fluid, however, may become absorbed during the weeks of waiting, and there may be radiological

evidence of a primary tuberculous complex as the lung becomes visible The effusion will only need to be aspirated when it is causing symptoms of pressure, or when it does not show evidence of clearing Treatment of the underlying primary complex must be instigated.

Disseminated lesions

Tuberculous disease in childhood is much more likely to be less localized than in adult life and, although primary lesions are usually in the thorax, the possibility of extension of the disease by the blood-stream has to be borne in mind so long as the primary pulmonary lesion is active Miliary tuberculosis, with or without meningitis, may develop , the chances of its occurrence are greater among infants and in children who have extensive involvement of pulmonary or lymphatic tissue

In supervising a child with primary tuberculosis, it is therefore necessary to keep a watch for early signs of meningitis or miliary tuberculosis, for prompt treatment with streptomycin may save the life of the child

Less dramatic results of blood-stream infection are the occurrence of lesions in other organs, such as bones, joints, kidneys or skin, all of which may either have their onset at the time of the active stage of the primary lesion or may not become manifest until a much later date Erythema nodosum is a not infrequent skin manifestation

MANAGEMENT AND TREATMENT OF PRIMARY TUBERCULOUS LESIONS

Any child found for the first time to be tuberculin-positive, especially if recent infection is suspected, should be kept under supervision, and a radiograph should be taken at 3-monthly and then 6-monthly intervals, until it is evident that no gross lesion is developing or that healing of the lesion is taking place. Apart from this precaution, no special treatment is indicated for primary lesions which take the normal course

Treatment of tuberculous broncho-pneumonia

Children who are acutely ill require skilled nursing and special care with feeding, so that sufficient nourishment may be provided throughout what is often a long illness Streptomycin, together with *para*-aminosalicylic acid, has been used in treating these cases Although it is early as yet to be dogmatic about results of treatment in a condition which may resolve spontaneously, it appears that this form of treatment is of definite benefit, both in preventing a fatal outcome and in [illegible] the length of the illness

tion of the lesion, or at least until there is no pyrexia and until there is a steady gain in weight. This may mean a period of months, so an important part of the treatment is the provision of entertainment and, for older children, of education Streptomycin together with *p*-aminosalicylic acid may be of advantage, but its effect is probably less spectacular than in the acute cases It is, of course, important to give *p*-aminosalicylic acid with streptomycin ; otherwise, if streptomycin is

given alone, there is a danger of producing strains of tubercle bacilli which are resistant to streptomycin, and therefore of throwing away a valuable weapon for dealing with a miliary infection, should that complication arise. The administration of *p*-aminosalicylic acid to children is made much easier than formerly by the use of enteric-coated granules.

Treatment of tuberculous hilar adenitis

Whatever the complication arising from tuberculous hilar adenitis, it is important to direct treatment primarily to the healing of the caseous mass of glands By encouraging the healing of the glands, it may be possible to minimize the risk of spread of tuberculous infection to the blood stream, or to other parts of the lung by aspiration, and it will also increase the likelihood of re-expansion of a lung already collapsed Whenever there is hilar adenitis sufficient to produce any clinical symptoms, or gross enlargement seen in the radiograph, or collapse of a segment of lung, the child should be kept in bed, as much at rest as is possible This period of rest should be continued, as in the case of broncho-pneumonia, until there are steady gain in weight, absence of pyrexia and improvement in the radiological findings

When part of the lung is collapsed, special treatment, directed to the re-opening of a blocked bronchus, has to be considered Bronchoscopy, with removal of granulation or tuberculous gland material in the lumen and with suction of secretions beyond, is advocated by some physicians. Re-expansion of the collapsed portion of the lung results in some cases, but there may be a recurrence of collapse, and the possibility of spreading the tuberculous infection has to be borne in mind, as has that of laying open the part of the lung involved to added non-tuberculous infection Since, in a large number of cases, the lung re-expands after a period of months, or 1–2 years, when the glandular lesion heals, treatment should be concerned primarily with the healing of the tuberculous lesion in the lymphatic glands

In order to lessen the chances of the development of bronchiectasis, upper-respiratory infections should be dealt with when they occur

PREVENTION

B.C.G. inoculation

The aim of inoculation with bacillus Calmette-Guérin vaccine (B C G) is to produce a controlled primary lesion in previously uninfected persons By so doing, the risk of the development of an overwhelming primary pulmonary lesion is lessened, and it is presumed that, if the inoculation is followed by a positive tuberculin reaction, increased immunity to tuberculous infection results

Inoculation is obviously of greatest value for persons exposed to special risk of infection, such as those in contact with open cases of tuberculosis, and for the age-groups in which primary infection is most likely to give rise to tuberculous disease ,

For ma

(Birkhaug

carried out in the United States of America by Rosenthal, Blahd and Leslie, in 1945

The B C G (bacillus Calmette-Guérin) vaccine is prepared from a strain of

attenuated bovine tubercle bacillus A murine type of bacillus (vole bacillus) is also being tested but is not yet available for general use

Technique of inoculation into the skin

Oral administration of B C G has not proved satisfactory and inoculation into the skin is the method practised at present This is carried out by means of the multiple-puncture method (Rosenthal, Blahd, and Leslie, 1945), by scarification, or by intradermal injection

Multiple puncture—For the multiple-puncture method, the skin is smeared with B C G vaccine (3 5–9 milligrams per millilitre) and is pricked with a needle in 30–60 places A modification of this technique has been introduced by Birkhaug (1944) who applies a perforated disc through which 40 needles pass when a spring is released and penetrate the skin to a given depth

Scarification—The scarification technique is similar to that used for smallpox vaccination and for this B C G vaccine, 20 milligrams per millilitre is used

Intradermal injection—For the intradermal injection, 0 1 millilitre of vaccine is injected strictly intradermally, usually in the deltoid region or in the anterior aspect of the thigh There is no constitutional disturbance following the inoculation, and there is little change at the site of injection until after 3 weeks, when redness and induration develop This is usually followed by slight ulceration and some discharge A scab forms after an interval varying from a few days to several weeks, and the lesion gradually heals leaving a small " tissue-paper " scar There may be palpable enlargement of the lymphatic glands draining the area at the height of the reaction

Preliminary testing

Before inoculation it is important to carry out satisfactory tuberculin tests to confirm that no previous infection has taken place Children should be tested if possible by the Mantoux test up to 1 0 milligram (1 100 O.T.) but the tuberculin-jelly test may have to suffice in some cases

It is recommended that, after a negative reaction has been obtained, the child should be isolated from any known source of tuberculous infection for 6 weeks before inoculation and re-tested after that period in order to avoid the possibility of inoculation during a time when allergy is developing It is also recommended that there should be strict isolation from infected persons for 6 weeks after inoculation, that is, while hypersensitivity is developing (Ministry of Health, 1949) It is not always possible to carry out strict isolation although some modification of the method recommended is usually possible

Reactions and immunity

Hypersensitivity to tuberculin usually develops between 4 and 6 weeks after inoculation and a further tuberculin test should be carried out after this interval Those few cases (about 2 per cent) in which positive reactions do not develop will require a second vaccination

Hypersensitivity tends to decrease after 18 months to 2 years in young children who do not become re-infected from outside sources, routine tuberculin tests should be carried out at yearly intervals after inoculation

Inoculation with B C G should not be considered to give protection against repeated heavy infection with tuberculous material, and successful inoculation should not be an excuse for relaxing precautions against avoidable infection.

REFERENCES

Birkhaug, K (1944) "Protective Value of the Intracutaneous and Percutaneous Methods of B C G Vaccination" *Acta med scand*, 117, 274

— (1947) "B C G Vaccination in Scandinavia" *Amer Rev Tuberc*, 55, 234

Blacklock, J W. S. (1932) "Tuberculous Disease in Children" *Med Res Coun Spec. Rep Ser*, No. 172

Brock, R C, Cann, R J., and Dickinson, J R (1937). "Tuberculous Mediastinal Lymphadenitis in Childhood, Secondary Effects on the Lungs" *Guy's Hosp. Rep*, 87, 295

Crowe, M P (1942) "Tuberculin Testing of 10–15-years-old Children in the Country" *Brit med J*, 1, 266

Deane, E H W (1946) "Comparison between Sensitivity of Tuberculin Tests" *Lancet*, 1, 162

Ghon, A (1916) *Primary Lung Focus of Tuberculosis in Children* London; Churchill

Hart, P d'A (1929) "Tuberculin Testing in 16-year-old London Children" *Med. Res Coun Spec Rep Ser*, No 164

Lloyd, W E, and Dow, D (1931) "Tuberculin Testing of Children at 10–14 years. *Brit med J*, 2, 1830

Macpherson, A M, and Lutwyche, V U (1950) "Pulmonary Collapse Associated with Primary Tuberculous Lesions" *Thorax, Lond*, 5, 1

Ministry of Health (1949) *B C G Vaccination*. Memorandum 322 B C G

Parrot, J M J (1876) "Communique le resultat de ses recherches sur les relations qui exister entre les lesions des pulmones et celles des ganglions trachéo-bronchiques" *C R Soc Biol*, 28, 308

Prophit Tuberculosis Survey (1948) "Tuberculin Testing of Navy Boys 15–16 years of Age" In *Tuberculosis in Young Adults*, p 33 London Lewis

Pointon, D W (1950) "Value of Tuberculin Jelly Test" *Brit med J*, 2, 1410

Rich, A R (1944). *The Pathogenesis of Tuberculosis*, p 212, Springfield Ill Thomas

Rosenthal, S R Blahd, M, and Leslie, Eleanor I (1945) "Ten Years' Experience with B C G." *J Pediat*, 26, 470

Schlesinger, B, and Hart P d'A. (1930) "Tuberculin Testing of London Children" *Arch Dis Childh, Lond*, 5, 191.

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ACUTE DISSEMINATION

In certain instances, principally among primitive races, in which resistance is negligible and multiplication of bacilli rapid, generalization is seen in a highly acute or septic form characterized by considerable fever and the appearance of tuberculous abscesses scattered throughout the body. The disease pursues a short and fatal course. In more resistant stock, such for example as of Western Europe, the absolute inability to put up any form of defence is rarely met with and acute generalization is correspondingly less fulminant.

Acute *miliary* tuberculosis

The lungs, and other organs, become studded with minute tuberculous foci which progress, develop, and finally coalesce. It is mainly a disease of children and in many examples a history of contact with a tuberculous parent, or other person, can be elicited. The relationship of the disease to the initial infection can often be traced by the demonstration of the primary focus with enlargement of the regional lymph glands, seen either on a skiagram during life or at autopsy.

Symptoms are constitutional and often indefinite at onset while physical signs are absent in the early stages, the illness presenting as pyrexia of undetermined nature. Later, fine crepitations may be heard scattered throughout the lungs. In the early stages x-ray evidence may be lacking, the characteristic pin-point stippling only appearing as the disease advances. Little reliance can be placed on the Mantoux test for a positive reaction may be abolished by the virulence of the infection. In severe examples of acute miliary tuberculosis the resemblance to typhoid fever may be close and only detailed laboratory studies will serve to decide between them. In this typhoidal form fever is considerable and sustained, the pulse full and relatively slow, and toxaemia pronounced with delirium preceding coma. The spleen is palpable, discrete spots appear on the trunk, and leucopenia may be found. In other examples—the meningeal form—cerebral signs and symptoms dominate the picture and in the absence of prompt specific treatment death results from tuberculous meningitis within 2 or 3 weeks.

Some of the difficulties in diagnosis have already been mentioned; another source of error is the rarity with which tubercle bacilli are found early in the disease. The radiological appearance, once it has become well-defined, does not as a rule cause difficulty; the diffuse uniform distribution of minute foci is characteristic. If in addition the primary focus itself is visible or the mediastinal glands enlarged, particularly the paratracheal group, there is little room for doubt. In adults in whom evidence of active initial infection may be absent, other causes of miliary mottling must be excluded (*see page 298*).

The portal of entry of the bacilli in acute miliary tuberculosis is variable. In the majority of examples it is obvious; in others it cannot be made out with certainty even by a most painstaking dissection at autopsy. The close association in infants and young children between the primary complex and miliary dissemination has formed the basis for the classification adopted by Dorothy Price (1942). The primary focus in the lung may be the source of bacilli reaching either the pulmonary vein, and so through the left auricle to the general circulation giving rise to widespread seedings, or the pulmonary artery causing a more localized lesion in the lung itself. Alternatively, the regional glands may fail to act as an efficient barrier

CHAPTER 12

HAEMATOGENOUS TUBERCULOSIS OF THE LUNGS

N LLOYD RUSBY

THE SPREAD of tuberculosis by the blood stream is a significant event in the natural evolution of the disease Although clearly recognized for many years it is only in comparatively recent times that the frequency, extent, and extreme variability of this mode of transmission has been fully disclosed by the correlation of autopsy studies with the clinical and radiological evidence obtained during life. This chapter will be concerned mainly with the manifestations of the disease in the lungs, and the implication of other organs of the body will be mentioned only in so far as this is relevant

Haematogenous dissemination is most common and is seen in its most severe form in infancy and early childhood when it can be directly related, in most instances, to the initial infection As age advances the tendency to generalization becomes less evident, but it remains as a potential sequel to the initial infection throughout life It is not confined, however, to the first infection, or to the few months immediately following it, but can take place during the course of the adult form of reinfection phthisis when its effects graduate from minimal deposits giving rise to no clinical signs to metastases so widespread, or vitally situated, as to cause death Wilson (1933) has investigated the question of tuberculous bacillaemia by culture and animal inoculation and found, by the methods then employed, a positive result in 5–10 per cent of those persons with advanced, severe and progressive pulmonary tuberculosis, in 30–40 per cent of examples of miliary tuberculosis or tuberculous meningitis, and from the heart blood at autopsy in 50 per cent of those who died of the disease When it is remembered that bacillaemia is often transitory and short-lived, though it may be repetitive, it will be evident that this work probably underestimates the incidence of blood stream invasion.

It has already been stated that the manifestations of blood-borne dissemination may vary between wide extremes of severity There are several factors which are held to influence the course of the disease, and these are the number of bacilli which gain access to the blood stream, single or repetitive seeding, the degree of natural or acquired resistance of the individual as a whole, local " organ " resistance, and theoretically, because it has not yet been convincingly proved, the virulence of the bacilli themselves The site of entry of the bacilli is also of some importance, for it may determine the organ affected and hence the consequences of invasion Taking these factors into consideration it becomes possible to delineate certain well-established examples of the disease whose place in the natural evolutionary order is clearly defined. The more acute the process the easier it is to do this; in the more chronic and restricted varieties the evidence becomes far less tangible, while in some the pronouncement that the disease is even haematogenous at all may be largely based on circumstantial evidence or speculation

ACUTE DISSEMINATION

In certain instances, principally among primitive races, in which resistance is negligible and multiplication of bacilli rapid, generalization is seen in a highly acute or septic form characterized by considerable fever and the appearance of tuberculous abscesses scattered throughout the body. The disease pursues a short and fatal course. In more resistant stock, such for example as of Western Europe, the absolute inability to put up any form of defence is rarely met with and acute generalization is correspondingly less fulminant.

Acute miliary tuberculosis

The lungs, and other organs, become studded with minute tuberculous foci which progress, develop, and finally coalesce. It is mainly a disease of children and in many examples a history of contact with a tuberculous parent, or other person, can be elicited. The relationship of the disease to the initial infection can often be traced by the demonstration of the primary focus with enlargement of the regional lymph glands, seen either on a skiagram during life or at autopsy.

Symptoms are constitutional and often indefinite at onset while physical signs are absent in the early stages, the illness presenting as pyrexia of undetermined nature. Later, fine crepitations may be heard scattered throughout the lungs. In the early stages x-ray evidence may be lacking, the characteristic pin-point stippling only appearing as the disease advances. Little reliance can be placed on the Mantoux test for a positive reaction may be abolished by the virulence of the infection. In severe examples of acute miliary tuberculosis the resemblance to typhoid fever may be close and only detailed laboratory studies will serve to decide between them. In this typhoidal form fever is considerable and sustained, the pulse full and relatively slow, and toxaemia pronounced with delirium preceding coma. The spleen is palpable, discrete spots appear on the trunk, and leucopenia may be found. In other examples—the meningeal form—cerebral signs and symptoms dominate the picture and in the absence of prompt specific treatment death results from tuberculous meningitis within 2 or 3 weeks.

Some of the difficulties in diagnosis have already been mentioned; another source of error is the rarity with which tubercle bacilli are found early in the disease. The radiological appearance, once it has become well-defined, does not as a rule cause difficulty; the diffuse uniform distribution of minute foci is characteristic. If in addition the primary focus itself is visible or the mediastinal glands enlarged, particularly the paratracheal group, there is little room for doubt. In adults in whom evidence of active initial infection may be absent, other causes of miliary mottling must be excluded (*see page 298*).

The portal of entry of the bacilli in acute miliary tuberculosis is variable. In the majority of examples it is obvious; in others it cannot be made out with certainty even by a most painstaking dissection at autopsy. The close association in infants and young children between the primary complex and miliary dissemination has formed the basis for the classification adopted by Dorothy Price (1942). The primary focus in the lung may be the source of bacilli reaching either the pulmonary vein, and so through the left auricle to the general circulation giving rise to widespread seedings, or the pulmonary artery causing a more localized lesion in the lung itself. Alternatively, the regional glands may fail to act as an efficient barrier

to the spread of infection in acute disease, the bacilli pouring directly into the thoracic duct and so to the venous system, the lungs bearing the main brunt of the infection The lungs may, in fact, succeed in sparing the general circulation by acting as a capillary filter, a mechanical barrier which may be fully effective, or only partially if the number of bacilli is great Direct erosion of a blood vessel by an enlarged caseating gland has often been demonstrated at autopsy and the organs picked out for dissemination in this way depend upon the particular vessel involved Pagel (1948) believes that in many cases blood-borne metastases result from a specific lesion of the walls of blood vessels themselves, a tuberculous endangiitis The lesion arises in the intima and can be distinguished from an attached thrombus by the unusually large number of bacilli contained within it and by the liquefaction which it undergoes The argument that such a vascular focus is the result of dissemination and not the cause of it has been at least partially refuted by the fact that in some examples studied it is clearly at a more advanced stage of development than the metastatic foci demonstrated in other organs of the body A similar specific involvement of the wall of the thoracic duct has also been described From either of these two sources bacilli can easily reach the main blood stream Finally, a discussion upon the mode of transmission of generalized disease would be incomplete without reference to the influence of trauma for there is little doubt that widespread metastases can follow manipulation of a tuberculous joint, curettage of a tuberculous endometrium, and even operations upon the lung itself.

It will be evident that from whatever source the bacilli are derived the pathological and clinical pattern finally assumed depends on the interplay of those factors enumerated above irrespective of the particular vessel or channel involved

Chronic miliary tuberculosis

Before specific treatment was available acute dissemination of tuberculous disease was almost invariably fatal ; yet for over a century it has been appreciated that the acute onset could be surmounted and the disease enter a chronic phase. It is only during the last 20 or 30 years, however, that the subject has been brought prominently into the foreground by the publication of individual case reports, many of which were made possible by the more widespread use of routine chest radiography [illegible] in a paper which [illegible] ding [illegible] tain described an example of healed (calcified) miliary tuberculosis of the lungs in a girl aged 8½ years which he regarded as exhibiting a form of haematogenous spread intermediate between the primary focus and miliary tuberculosis of the lungs. Burton Wood (1933) and Deaner (1935) contributed additional examples, and knowledge of the subject was further extended by the important monograph by Hoyle and Vaizey (1937) and the work of Fish (1937)

Hoyle and Vaizey collected from the literature 120 examples which satisfied their strict criteria of diagnosis and added 10 more which they had personally observed. No case which failed to survive for three months or longer was included. These authors emphasized the difficulties of diagnosis and drew attention to the distinction between haematogenous invasion and the lymphogenous form, to which reference



FIG 114—Male 37 years, admitted for reconstruction arthrodesis for tuberculosis of right hip joint Multiple punctate calcified deposits scattered more or less uniformly throughout both lung fields Also [illegible] is an
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will be made later Their paper clearly illustrates the often protracted nature of the condition and the possible modes of termination

Fish presented a clinical account of 10 examples of the disease which he had studied at Highwood Hospital for children, 6 of which were fatal within from 5½ to 10 months from onset, the remaining 4 recovering He was unable to draw any clear line of delineation between acute fulminant miliary tuberculosis and the chronic variety, there being every degree of gradation between them In the fatal cases tubercles of all ages were demonstrable implying multiple successive crops, and he believed that each episode of dissemination was accompanied by bouts of fever He made two further important observations First, that 8 out of the 10 cases showed a widened mediastinum due to enlargement of the paratracheal group of glands and drew the inference that the route of dissemination was by the thoracic or right lymphatic duct The two instances in which this mediastinal widening was not seen had sustained only one episode of dissemination and no recurrence of bacillaemia as far as could be judged Secondly, without exception, the four cases which recovered at some time exhibited extra-pulmonary tuberculous lesions that could only have arisen from the transmission of bacilli by the blood stream

Chronic miliary tuberculosis is thus an established fact The disease may result

to the spread of infection in acute disease, the bacilli pouring directly into thoracic duct and so to the venous system, the lungs bearing the main brunt of infection The lungs may, in fact, succeed in sparing the general circulation acting as a capillary filter, a mechanical barrier which may be fully effective, only partially if the number of bacilli is great. Direct erosion of a blood vessel by enlarged caseating gland has often been demonstrated at autopsy and the org picked out for dissemination in this way depend upon the particular vessel involv Pagel (1948) believes that in many cases blood-borne metastases result from specific lesion of the walls of blood vessels themselves, a tuberculous endangii The lesion arises in the intima and can be distinguished from an attached thromb by the unusually large number of bacilli contained within it and by the liquefactio which it undergoes The argument that such a vascular focus is the result dissemination and not the cause of it has been at least partially refuted by the fa that in some examples studied it is clearly at a more advanced stage of developmen than the metastatic foci demonstrated in other organs of the body A simil specific involvement of the wall of the thoracic duct has also been described Fron either of these two sources bacilli can easily reach the main blood stream Finally, a discussion upon the mode of transmission of generalized disease would b incomplete without reference to the influence of trauma for there is little doubt tha widespread metastases can follow manipulation of a tuberculous joint, curettage o a tuberculous endometrium, and even operations upon the lung itself.

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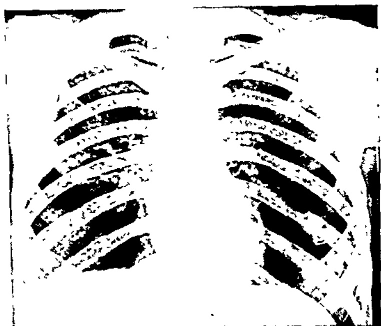


FIG 115—Chronic miliary mottling with a cavity in the apex of the right lower lobe in a woman aged 20 years The miliary shadows eventually disappeared but the cavity persisted She died 3 years later of Addison's disease of the suprarenal glands.

on streptomycin a full investigation of the urinary tract was carried out and the right kidney removed (Mr Neligan) At the time of her discharge to sanatorium after six months in hospital the chest film was absolutely clear except for some minimal "abortive" foci at both apices, and the urine was sterile on culture for tubercle bacilli Towards the end of 1949 she was again found to be passing bacilli in the urine, developed severe pain in the back, and is now under treatment for Pott's disease of the spine

This subject cannot be dismissed without reference to miliary calcification in the lung fields. This has sometimes been found during the performance of a routine autopsy, or occasionally as the result of routine radiography, and is compatible with good health Terplan (1945) found nearly 200 parenchymatous calcified tubercles as an incidental post-mortem finding in a 60-year-old male, associated with calcified deposits in liver, spleen and kidneys Certain structural distinctions suggested that not all the pulmonary nodules were of the same age Such a finding could very easily be due to chronic miliary tuberculosis which had healed in this way and which had been the result of successive crops But such an assumption at once demands an answer to two questions . is calcification in the lungs always the result of tuberculosis ; and if it is due to tuberculosis what is the evidence that it is haematogenous in origin ? Until lately the answer to the first question would probably have been that, with the exception of certain extremely rare conditions, such as calcified cysts or phleboliths or the occurrence of metastatic calcification

from obvious acute miliary disease of the lungs, or it may be discovered radiologically when blood-borne dissemination has never been clinically suspected Diagnosis is largely radiological (Fig 114) The foci are often larger and coarser in texture than in acute miliary disease, but it is often difficult from an inspection of one film alone and without taking all the features of the case into consideration to decide into which category a particular example should be placed Differential diagnosis must take into account a number of other disorders which cause a miliary type of mottling on an x-ray film A full list of these is given in Hoyle and Vaizey's monograph Among the acute conditions which must be remembered are acute tuberculous broncho-pneumonia, disseminated broncho-pneumonia, and pulmonary [illegible] diffuse car[illegible] sha[illegible] (gu[illegible]

cases the disease proves fatal within 6–12 months , in others, after a longer period of quiescence, relapse occurs and death results from generalized disease, often with a terminal tuberculous meningitis Congestive cardiac failure may supervene There is no doubt, however, that the miliary foci in the lungs can heal and leave no trace, or the foci can become converted into calcified deposits which are presumably inactive. Even those fortunate subjects in whom the disease in the lungs apparently heals, remain liable to develop extra-pulmonary foci at any time subsequently, even up to several years, as the following example shows :

Case 1—C D , a single woman aged 23 years, was admitted to the London Chest Hospital for the treatment of a right lower lobe tuberculous cavity. Seven years previously she had spent two years in Black Notley Hospital for a tuberculous infection of the right knee joint and was discharged in January, 1943. In October, 1945, she was readmitted with an abscess behind the knee Chest radiograph at this time showed diffuse evenly distributed disease of a coarse miliary type and a right lower lobe cavity (Fig 115) With rest the miliary opacities slowly disappeared although a left-sided pleural effusion developed in 1946 This also cleared up The knee joint was excised in September, 1946 On admission to the London Chest Hospital in 1948 the lungs were free of disease, radiologically, except for the lower lobe cavity. Before treatment could be planned she sought her discharge for urgent domestic reasons She was readmitted as an emergency two months later with symptoms of Addison's disease of the suprarenals from which she died 48 hours later, resisting all treatment At autopsy both suprarenals were found completely destroyed by caseation

It is probably too early yet to assess the ultimate influence of antibiotic therapy upon this class of disease It may enable a proportion of these patients to attain quiescence who might not otherwise do so, and may also reduce the risk of subsequent breakdown or of delayed metastatic dissemination That acute miliary disease, rendered first chronic and later apparently healed by streptomycin, is not necessarily relieved of this risk is clear from the following case history :

Case 2—N O'B , a married woman, Irish, aged 24 years, was admitted to the London Hospital in the early part of 1947 with the typical picture of acute miliary tuberculosis of the lungs She was passing bacilli in the urine The sputum was consistently negative She was treated with streptomycin, receiving a 4 month course of 2 grammes daily at the beginning, later reduced to 1 gramme daily She responded favourably and while

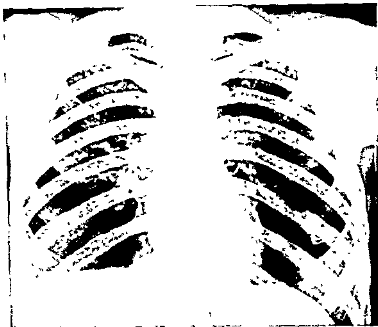


FIG. 115.—Chronic miliary mottling with a cavity in the apex of the right lower lobe in a woman aged 20 years. The miliary shadows eventually disappeared but the cavity persisted. She died 3 years later of Addison's disease of the suprarenal glands.

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in the lung in association with chronic nephritis as described by Barnard (1946), calcification in the lung should be regarded as tuberculous in nature Indeed, tubercle bacilli have been found within these deposits and certainly the presence of similar foci in distant organs lends force to this argument To the best of our knowledge this answer is still largely true for Great Britain today ; but in certain districts of the United States of America an additional and not uncommon source of calcified deposits in the lung has been traced to a fungus infection, histoplasmosis. At the time of writing only isolated accounts of histoplasmosis occurring in Great Britain have been published

The second problem, that of deciding whether or not such calcified deposits are haematogenous in origin, is a most difficult one to settle absolutely Max Pinner (1934) some years ago held decided views on this point and wrote these words : "with the exception of true primary foci it seems that calcification occurs only in foci of haematogenous origin Why this should be so is unexplained, but in thousands of roentgen series in adults, calcification was never seen to develop, unless the original lesions were definitely suggestive of the haematogenous type " This is a most interesting suggestion and due regard must be paid to it for it undoubtedly has some substance But there are difficulties in the way of accepting it unreservedly, for it is uncertain at present to what extent a retrospective inference of

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POST-PRIMARY HAEMATOGENOUS MANIFESTATIONS

It has already been observed that the time of the initial infection, or shortly after it, is the one at which dissemination of the disease is most to be anticipated and, depending upon various factors, such dissemination may be acute, subacute or even chronic and protracted in its course Occasionally such miliary dissemination may be restricted in extent to a small area of the lung field, generally at one or other apex —discrete miliary tuberculosis—and such a finding is a not uncommon accompani*ment of tuberculous pleural effusion The initial infection, however,* in most people is surmounted uneventfully without any clinical evidence of dissemination, and this is particularly true if it occurs later than the first 3–5 years of life. Nevertheless, it is probable that dissemination to the lungs takes place more often than is popularly supposed and does so silently without causing any clinical disturbance

One of the commonest of these post-primary manifestations is seen at the

generally benign, a small proportion later develop and excavate and so give rise to bronchogenic phthisis with positive sputum ; or they may show a tendency to *progress and extend downwards in the lung, again causing symptoms* of established disease

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It is appropriate at this point to mention the "tuberculoma" which consists histologically of a mass of tuberculous granulation tissue the central portion of which may be found caseous and liquefied. When occurring in the lung it is often an accidental finding and is revealed radiologically as a circumscribed spherical mass in the lung field, as a rule there are no attendant symptoms and it gives rise to no physical signs Its exact mode of origin is not clearly understood but the absence of symptoms suggests that it may be blood borne, as also does the occurrence of deposits of similar structure in remote organs such as the kidney, spleen, liver, and the brain It may also be the result of the development, up to a certain point, of a post-primary metastasis already described, or even the pulmonary component of the primary focus itself

The place in the natural evolutionary order of the disease that is occupied by tuberculous pleural effusion has been the subject of considerable discussion and cannot yet be regarded as finally settled It is admitted that an effusion may form over the primary focus in children and be directly dependent on it—the "benign effusion" of Burton Wood—and it has been shown that the pleura may be infected by contiguity from the mediastinal glands, it is likewise accepted that pleural effusion may be a complication of established phthisis although it is not very commonly seen It is on the "primary" or "idiopathic" pleural effusion, much the greater proportion of which are undoubtedly tuberculous in nature, that controversy centres It is believed that many examples of pleural effusion appear within a few months of the initial infection and this naturally raises the question as to whether they should be classified among the haematogenous post-primary disseminations. Moreover, it is not uncommon for an effusion on one side to be followed a month or two later by one on the opposite side, or both may occur simultaneously Pleural effusion not infrequently accompanies acute miliary tuberculosis of the lung In some instances more than one serous membrane may be involved, and a unilateral or bilateral effusion is found associated with ascites or a pericardial exudate Whatever may be the feeling about the relatively benign unilateral effusion, a good case can be made out for the haematogenous origin of its occurrence on both sides, and for those examples in which there is a more widespread involvement of the serous membranes Many authorities hold that pleural effusion in such instances results from the deposits of minute tuberculous foci in that narrow band of lung substance lying beneath the visceral pleura, known as the cortico-pleural zone The practical lesson is that pleural effusion should be regarded as possibly the forerunner of other manifestations of blood-borne disease such as exudates in other serous membranes, tuberculosis in distant organs, or even generalized miliary tuberculosis of the lungs and meninges, quite apart from the

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One of the commonest of these post-primary manifestations is seen at the extreme apex of the lung fields Such a focus, or group of foci, in most instances heals spontaneously and is seen on a radiograph as a calcified deposit, the so-called " Simon focus " An alternative name is the " abortive focus ". Although generally benign, a small proportion later develop and excavate and so give rise to bronchogenic phthisis with positive sputum , or they may show a tendency to progress and extend downwards in the lung, again causing symptoms of established disease

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disease is endogenous in origin This theory has certain attractions, but there are many difficult questions to be answered before it can be accepted as the invariable, or even the most probable, explanation for the origin of the ordinary form of reinfection pulmonary tuberculosis

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added risk which these subjects run of subsequently developing the more florid form of reinfection phthisis.

LUNG CHANGES IN EXTRA-PULMONARY FOCI

If the haematogenous origin of most extra-pulmonary tuberculous lesions is accepted, it might be possible to obtain some information about the type of pulmonary changes associated with such scattered disseminations by clinical and x-ray examination of the lungs of these patients

There have been several published surveys of the incidence of pulmonary disease in "surgical" tuberculosis For example Reisner (1934) investigated 240 patients, mostly adults, comprising 160 examples of skeletal disease, 66 of genito-urinary, and 14 in which serous membranes of the body were affected. In the material as a whole he found evidence of pulmonary disease, excluding the remains of the primary complex, in 124 cases (51 7 per cent) He classified these changes into several groups (1) Minimal or abortive lesions These accounted for 17 per cent of the 124 examples and consisted of sparsely scattered, often calcified, nodules in the lung apices (2) Chronic disseminated lesions, which accounted for 24·2 per cent of the series The form of the disease in this group was bilateral and symmetrical in distribution, involving the upper zones more than the lower Emphysema was noted at the bases Symptoms were absent in about half of these cases and the sputum generally negative for tubercle bacilli (3) Chronic disseminated lesions similar to the preceding but exhibiting evidence of ulceration and cavitation Reisner found this type of disease in 17 per cent of the cases In contrast to the preceding group, symptoms were present and the sputum positive in most of these patients. (4) Terminal acute dissemination was seen in 8 per cent In some this followed operative procedures The remaining examples, amounting to 33 8 per cent of t[illegible] series, exhibited the characteristics of the ordinary form of bronchogenic phthis[illegible] and were further subdivided into caseous pneumonic, cirrhotic, and benign exuda[illegible] tive forms Thus in 82 out of the 124 patients showing pulmonary involvement (66 2 per cent or groups 1 to 4 above) the disease presented certain features which were unlike bronchogenic phthisis as ordinarily seen Reisner believes that in these 82 patients the pulmonary disease was haematogenous

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the chest were inconspicuous, yet the radiological extent of the disease was considerable and corresponded to the "ground glass" pattern. It is curious that in these patients the extrinsic parts of the larynx—the epiglottis, aryepiglottic folds, and arytenoids—are chiefly affected. The prognosis in the absence of specific treatment is not good and collapse therapy is rarely successful, but the outlook has materially altered for the better since streptomycin has been used. The following case history will serve as an example.

Case 3—T A, married woman, aged 30 years, seen in the out-patient department of the London Hospital in March, 1950. In November, 1949 an ulcer was excised from the centre of the tongue which had been present for nearly one year and which was

writing the larynx and her general condition have improved beyond recognition and the x-ray changes are beginning to clear.

Examples of this type of disease can also be found in skeletal and genito-urinary tuberculosis.

Case 4—D M, a married woman aged 30 years, had left-sided pleurisy in 1938, and in 1939 was under treatment for tuberculous peritonitis and salpingitis. In 1940 she was admitted to Black Notley Hospital for tuberculosis of the spine. She had three separate lesions in the vertebral column. There were practically no chest symptoms and such sputum as was produced was at first negative for tubercle bacilli, later becoming positive. X-ray examination of the chest in July, 1940 shows extensive disease in the upper one-third of both lungs (Fig 117*a*). An enlargement of the left upper zone (Fig. 117*b*) brings out more clearly the diffuse nature of the change and the "ground glass" effect.

She received prolonged treatment for her spine and made a good recovery. Fig 118*a* and *b* show the state of the lungs in May, 1947, the disease has almost completely cleared and punctate deposits of calcification can be seen in the left upper zone.

Case 5—S H, male, aged 22 years, had tuberculosis of the right elbow joint in 1945. Apart from some breathlessness which was of long standing there were no

is slowly clearing and that calcification is occurring at both apices.

The evidence which has led to the belief that these manifestations in the lung are haematogenous in origin demand a brief recapitulation.

(1) The character of the x-ray appearance in the early stages is essentially *different* from fibrocaseous tuberculosis of bronchogenic origin. Later, as has been remarked, this characteristic may become masked and the change exceedingly difficult to interpret correctly. Furthermore, the great disproportion between the

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In 1934 Max Pinner reported on 28 cases of pulmonary tuberculosis (14 of which came to necropsy) which in his view differed from the usual bronchogenic phthisis. He gave an account of the x-ray characteristics of this group. The upper zones were symmetrically invaded by soft fluffy areas with blurred borders, fairly homogeneous in structure but varying considerably in size. The foci were not clear-cut like miliary deposits but were joined by "stringy lines". Pinner noted also the gross disproportion between the extent of the x-ray change and the degree of clinical symptoms and signs, which were meagre. This finding influenced him in expressing the view that this type of disease was haematogenous in nature. There is little doubt that this entity is similar to, if not identical with, that described by Reisner (group 2, page 302) as chronic disseminated tuberculosis and which he found in 24 2 per cent of those patients in his series who had both extra-pulmonary lesions and lung changes. Wilkinson also observed it in 3 out of the 47 patients with genito-urinary tuberculosis which he studied.

In the early stages the lung change is almost invariably a radiological discovery. The abnormality is extensive and involves the upper one-half or two-thirds of the lung fields. It is bilateral and curiously symmetrical in distribution. The shadows differ from chronic miliary tuberculosis in that the individual foci are less clear-cut and more diffuse, and are connected to one another by fibrils or strands which impart a reticulation to the affected area. The expression "ground glass" or "frosted glass" has been aptly applied to it. The essence of the change is difficult to reproduce convincingly and only a close study of the film itself will demonstrate it at all vividly. If the disease is progressive the individual foci coalesce and come into communication with a bronchus, cavitation will result, and bronchogenic spread follows which may so alter the x-ray appearance as to render the original distinctive pattern no longer recognizable.

On the purely clinical side the most remarkable features of this type of tuber- ... the early stages

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Davis and Wilson (1938) drew attention to certain examples of tuberculous laryngitis which were accompanied by a distinctive x-ray appearance of the chest, and from their description of the film there seems little doubt that they were observing the particular type of x-ray change under discussion. A G Cohen ... examples of haematogenous disease in which the presenting ...

disease without respiratory symptoms. These patients were ... clusively, male in the middle period of life, laryngeal symptoms were complained of for some months very often before chest symptoms became added, physical signs in

the chest were inconspicuous, yet the radiological extent of the disease was considerable and corresponded to the " ground glass " pattern. It is curious that in these patients the extrinsic parts of the larynx—the epiglottis, aryepiglottic folds, and arytenoids—are chiefly affected The prognosis in the absence of specific treatment is not good and collapse therapy is rarely successful, but the outlook has materially altered for the better since streptomycin has been used The following case history will serve as an example ·

Case 3—T A, married woman, aged 30 years, seen in the out-patient department of the London Hospital in March, 1950 In November, 1949 an ulcer was excised from the centre of the tongue which had been present for nearly one year and which was surprisingly free of pain It was proved histologically to be tuberculous In December, 1949, she complained of sore throat, and laryngoscopy revealed considerable oedema of the epiglottis and arytenoids She had at no time complained of chest symptoms and up to this point had lost no weight An x-ray of the chest, however (Fig 116*a*), shows extensive involvement of both apices of the " ground glass " or " frosted " type and almost symmetrical on the two sides A magnified reproduction of the left upper zone (Fig 116*b*) shows the form of the disease to better advantage For the past three months she has had *para*-aminosalicylic acids and streptomycin and at the time of writing the larynx and her general condition have improved beyond recognition and the x-ray changes are beginning to clear

Examples of this type of disease can also be found in skeletal and genito-urinary tuberculosis

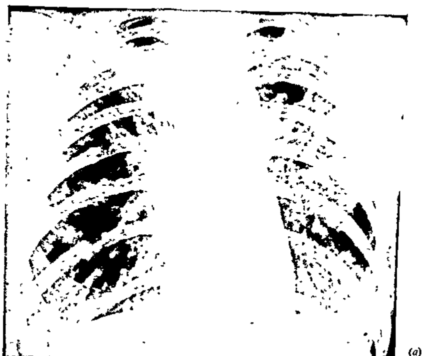
Case 4—D M, a married woman aged 30 years, had left-sided pleurisy in 1938, and in 1939 was under treatment for tuberculous peritonitis and salpingitis In 1940 she was admitted to Black Notley Hospital for tuberculosis of the spine She had three separate lesions in the vertebral column There were practically no chest symptoms and such sputum as was produced was at first negative for tubercle bacilli, later becoming positive X-ray examination of the chest in July, 1940 shows extensive disease in the upper one-third of both lungs (Fig 117*a*) An enlargement of the left upper zone (Fig 117*b*) brings out more clearly the diffuse nature of the change and the " ground glass " effect

She received prolonged treatment for her spine and made a good recovery Fig 118*a* and *b* show the state of the lungs in May, 1947 the disease has almost completely cleared and punctate deposits of calcification can be seen in the left upper zone

Case 5—S H, male, aged 22 years, had tuberculosis of the right elbow joint in 1945 Apart from some breathlessness which was of long standing there were no complaints referable to the chest He was putting on weight A radiograph of the chest in May, 1946 (Fig 119), shows diffuse bilateral symmetrical involvement of the upper one-third of the lung fields The opacity is of the reticulated pattern Sputum was consistently negative for tubercle bacilli In 1947 the elbow joint was excised X-ray examination of the chest in September, 1949 (Fig 120), shows that the opacity is slowly clearing and that calcification is occurring at both apices

The evidence which has led to the belief that these manifestations in the lung are haematogenous in origin demand a brief recapitulation

(1) The character of the x-ray appearance in the early stages is essentially different from fibrocaseous tuberculosis of bronchogenic origin Later, as has been remarked, this characteristic may become masked and the change exceedingly difficult to interpret correctly Furthermore, the great disproportion between the



(a)

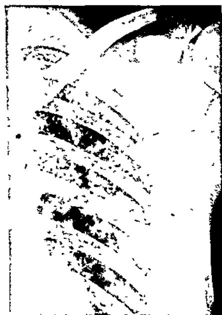


(b)

Fig 116—Bilateral infiltration of the "ground glass" pattern occurring in a woman, aged 30 years, in association [illegible]



(a)



(b)

FIG 117.—Bilateral, predominantly apical, symmetrical infiltration of the "ground glass" pattern occurring in a woman, aged 31 years, with tuberculosis of the skeletal and genito-urinary systems (July, 1940)

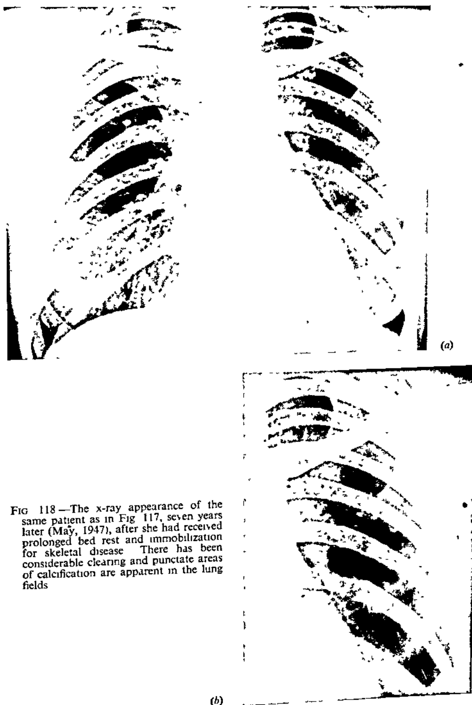


Fig 118—The x-ray appearance of the same patient as in Fig 117, seven years later (May, 1947), after she had received prolonged bed rest and immobilization for skeletal disease There has been considerable clearing and punctate areas of calcification are apparent in the lung fields



Fig 119—Diffuse, bilateral, symmetrical infiltration of upper one-third of lung fields in a male, aged 22 years, who had few if any symptoms of lung disease but admitted with tuberculosis of right elbow joint (May, 1946)

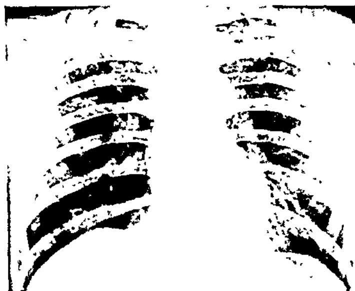


Fig 120—Same patient as Fig 119. State of lungs Sept 1949 The infiltration has partially cleared, is now more "formative" in character; calcified deposits are visible. No specific treatment had been used for the lungs.

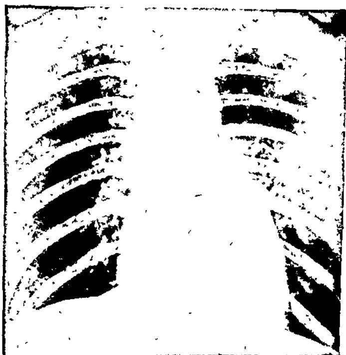


FIG 121.—Young man, aged 21 years, taken shortly after he had been admitted to an orthopaedic hospital (10th Nov., 1948), with tuberculosis of the right hip, right ulna and carpus. Later he developed synovial infection of the right knee joint. The film shows soft *diffuse disease at both* apices and denser infiltration in the left mid zone (*By courtesy of Dr B W Armstrong.*)

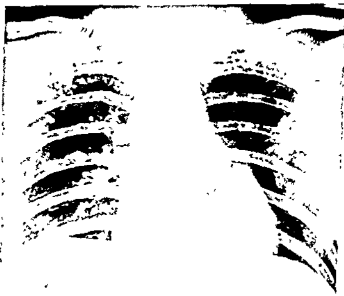


FIG 122—Same case as in Fig 121 (16th Feb, 1952), healing has taken place by calcification He received streptomycin shortly after his admission, and further courses later, but no other active treatment beyond complete bed rest which his skeletal disease necessitated It is probable that the left mid-zone lesion represents the initial infection, the apical disease post-primary haematogenous dissemination The films demonstrate the tendency to heal by calcification (*By courtesy of Dr. B W. Armstrong.*)

radiological extent of the disease and the symptoms, physical signs and general bodily condition of the patient is something foreign to pulmonary tuberculosis as usually seen

(2) Sputum is frequently absent and tests for tubercle bacilli often negative

(3) Histological examination points to the conclusion that the lesions are interstitial and are grouped round the blood vessels or lymphatics (Pagel, 1948) The emphysematous component has been demonstrated by Pagel The microscopical appearance may be radically modified later if bronchogenic phthisis supervenes It is probable that the interstitial nature of the process, and the emphysema which accompanies it, partly explains the absence of physical signs

(4) The response to streptomycin is often extremely satisfactory and this is in conformity with the response of haematogenous disease in general to the drug

(5) The frequent association with haematogenous manifestations outside the thorax

(6) The unmistakable tendency for the disease to heal by calcification has been advanced, especially by Pinner (1934), as a point of evidence in favour of a haematogenous origin

It must be admitted, however, that it is often exceedingly difficult, in any particular examples, to prove beyond doubt that the disease is blood borne Pinner has stated that it may be impossible to do so The possibility of this form of the disease being lymphogenous in origin must be considered That tuberculosis can spread along lymphatics from the mediastinal glands against the normal direction of the lymph was acknowledged by Pleininger (quoted by Fish, 1937), who described "lymphangitis reticularis tuberculosa" A similar mode of spread is occasionally seen in carcinoma Hoyle and Vaizey (1937) in their monograph described an example in the first case of their personal series This patient, aged 38 years, showed a diffuse reticular pattern in the chest radiograph which was most dense at the hilum No conclusive evidence of tuberculosis was found during life Death occurred from congestive cardiac failure Necropsy revealed a miliary granulomatous and fibrous lymphogenous tuberculosis with miliary haematogenous deposits in liver and spleen The x-ray appearance of this case, as far as can be judged from reproductions, is similar to that of chronic diffuse emphysematous tuberculosis but there are certain differences In the lymphogenous form, for example, the density appears greatest around the lung root and spreads fan-wise into the lung fields, in the chronic diffuse emphysematous form the change is maximal at the apices and symmetrical, thinning out as the mid or lower zones are approached In some examples of reticular change evidence of enlargement of the mediastinal glands is found which suggests a lymphogenous mode of spread Further research is required before this question can be regarded as settled

PROGNOSIS AND MANAGEMENT

en before the discovery of streptomycin acute miliary tuberculosis of the lungs easionally passed into a subacute or chronic phase Often this phase is but short d and death takes place after a few months from reactivation in the lungs or meningitis In all forms of miliary tuberculosis of the lungs the danger of mination to other organs is constantly present. In early life generalization is

widespread ; in the adolescent period the skeletal system seems particularly vulnerable, while in middle age genito-urinary manifestations become increasingly common The serous membranes become implicated at any age, but possibly particularly so within 6–12 months of the occurrence of the initial infection in adolescence or young adulthood In some patients manifestations in more than one system of the body follow one another at intervals of a few years ; in others combined lesions are present from the beginning The whole process may be protracted over many years Follow-up studies suggest that disability and death are more often the result of these extra-pulmonary foci than of the lung disease itself, with meningitis and involvement of the suprarenals as those most to be feared

one

onl

There is no aspect of tuberculosis in which prevention is more important and a great deal of the effort expended towards safeguarding the community is directed against this form of the disease The close relationship between the initial infection in early life and acute generalization points to the importance of separating young children from the source of infection in the home and elsewhere The younger the child the more devastating often is the result of such infection and the greater the need therefore to break contact If there is delay in removing the " open " case to hospital for treatment the child should be removed from the home and boarded out, or if this cannot be done steps should be taken by explanation and persuasion to reduce the risk to a minimum Experience with the bacillus of Calmette and Guérin has shown that vaccination is a valuable preventive measure As soon as the occurrence of the primary complex is recognized in a young child and deemed worthy of treatment, rest under good conditions should be enforced

Streptomycin has favourably altered the prognosis and is proving of the greatest service in treatment Details of treatment are given elsewhere and lie outside the scope of this chapter, but it can be stated at this point that the active exudative lesions of haematogenous tuberculosis often respond dramatically to the drug and provide one of the most urgent indications for its use Streptomycin must be used, however, with discretion and caution in this as in other forms of tuberculosis, and does not abolish the need for general treatment such as rest under sanatorium conditions which may need to be enforced for a considerable time Collapse therapy is less often required in haematogenous tuberculosis than in fibrocaseous tuberculosis with cavitation In those varieties of the disease which progress and pass into the open bronchogenic form the need for collapse therapy must be judged on the individual merits of the case

Finally, a word must be said about the management of the patient with combined lesions It has already been seen that the disease can emerge as isolated yet consecutive incidents in various systems of the body, and each of these demands skilled judgment and treatment by experts in the particular speciality Yet in every instance the treatment must be related to the background of the infective process as a whole This principle has been clearly stated by Cleveland (1935) in a review of the surgical treatment of joint tuberculosis when he says : " the condition of the lungs, upper respiratory tract, gastro-intestinal tract, and genito-urinary tract is of

paramount importance in these patients who must be studied as a whole in relation to their tuberculous infection" Only too often it seems that the patient with isolated pulmonary tuberculosis suffers from too many masters ; he with combined lesions from too few There is no field which illustrates more clearly than haematogenous dissemination the unitary nature of tuberculous infection, and the ultimate success of treatment largely depends upon the pooled resources of a team

I desire to express my indebtedness to Mr M C Wilkinson, F R C S, of Black Notley Hospital for allowing me access to his material and for permission to reproduce cases which were under his care, and also to Dr J T Wright for his help in assembling some of the records

BIBLIOGRAPHY

Barnard W G (1946) "Calcification of the Lung Alveoli" *J Path Bact*, 58, 625

Burnand, R, and Saye, L (1924) "Granulies Froides et Granulies Chroniques" *Ann Med*, 15, 365

Cleveland, M (1935) "Surgical Treatment of Joint Tuberculosis" *Surg Gynec Obstet*, 61, 503

Cohen, A G (1940) "Haematogenous Tuberculosis with Involvement of the Larynx" *Amer Rev Tuberc*, 41, 426

Davis, S C, and Wilson, R A (1938) "Observations on Pulmonary Tuberculosis when Complicated by Laryngeal Tuberculosis" *Dis Chest* 4, 13

Deaner, S (1935) "A Case of Chronic Disseminated Pulmonary Tuberculosis with Erythema Nodosum" *Brit med J*, 1, 357

Fish, R H (1937) "Chronic Miliary Tuberculosis in Children" *Arch Dis Child*, 12, 1

Hoyle, C, and Vaizey, M (1937) *Chronic Miliary Tuberculosis* London, Oxford University Press

Mann, K J (1946) "Lung Lesions in Skeletal Tuberculosis" *Lancet*, 2, 744

O'Reilly, J N (1933–34) "Healed (calcified) Miliary Tuberculosis of the Lungs" *Proc R Soc, Med*, 27, 1333

Pagel, W (1948) *Pulmonary Tuberculosis*, 2nd ed Ed by G G Kayne, W Pagel and L O'Shaughnessy London, Oxford University Press

Pinner, M (1934) "Haematogenous (non-miliary) Pulmonary Tuberculosis" *Amer J. Roentgenol*, 31, 442

Price, Dorothy, S (1942) *Tuberculosis in Childhood* Bristol, Wright

Reisner, D (1934) "The Relation Between Extrapulmonary and Pulmonary Tuberculosis" *Amer Rev Tuberc*, 30, 375

Terplan, K (1945) "Anatomical Studies in Human Tuberculosis, XX" *Amer Rev Tuberc*, 52, 505

Wilkinson, M C (1937) "Tuberculous Lesions in Association with Genito-Urinary Tuberculosis" *Lancet*, 1, 314

Wilson, G S (1933) "Tuberculous Bacillaemia" *Spec Rep Ser Med Res Coun* No 182 London, H M Stationery Office

Wood, W B (1933) "Clinical Manifestations of Pulmonary Tuberculosis in Childhood" *Lancet*, 2, 797,

CHAPTER 13

BRONCHOGENIC TUBERCULOSIS

F. H Young

BRONCHOGENIC DISEASE

Although *the primary and haematogenous forms of tuberculosis when situated in the lungs, have special features as compared with tuberculosis in other organs, it is in the bronchogenic forms that the great difference occurs* These forms make up the bulk of the cases of chronic pulmonary tuberculosis It must, however, be emphasized that clinically the distinction between the bronchogenic form of the disease, *the late primary disease occurring in adults and adolescents*, and disease caused by haematogenous dissemination is frequently impossible (Israel and Longer, 1942) Apart from this, unless these forms heal, bronchogenic disease is superimposed on them This fact renders it difficult, if not impossible, for the pathologist to determine in which way any particular lesion started.

Aetiological factors

The appreciation of the vagaries of bronchogenic disease must take cognizance of the following facts

The presence of material containing tubercle bacilli, free in the bronchial system

There seem to be three possible sources from which tubercle bacilli can get into the bronchial tree

(i) From a cavity in the lung; it is quite unnecessary to demand that this should be demonstrable radiologically; many cavities are too small to be shown by this means

(ii) From an ulcer in the bronchus.
strable tuberculous bronchitis, but in th
of microscopic bronchial inflammation
and many lesions are beyond bronchoscopic vision

(iii) From the ulceration into the bronchus of a breaking-down tuberculous gland

(iv) From exogenous sources, by inhalation

The difference in the reaction of the lung tissue of different individuals

In addition to this there may possibly be variations from time to time in the same individual

Unless there is an appreciable resistance to the presence of the tubercle bacilli on the bronchial mucous membrane, it is obvious that, once tubercle bacilli are present in the bronchial tree, the tuberculous processes would proceed uninterruptedly to the death of the individual by a process of multiple aspiration and implantation of disease The part played by the scavenging process in the reduction in the time during which the contact takes place is of the greatest importance,

but, all things being equal, it is probable that personal resistance is the main factor which determines whether or not a lesion will occur.

The constant oscillations of pressure in the bronchi

In the normal lung, with each inspiration, a negative pressure is establish— in the bronchi In the potential space between the layers of the pleura there negative pressure of about 6 centimetres of water, and the pressure in the sm bronchi is of this order on inspiration On expiration the pressure approach the atmospheric level When coughing occurs the difference is much greate. If there is an impediment to free air-flow by a drop of sputum, this is furthe increased The oscillations are further complicated by the distortion and increased rigidity of the bronchi, which occur as the result of Nature's effort to heal the disease

The scavenging mechanism of the bronchi is normally extremely efficient. Hour by hour, day by day, the tuberculous material from a cavity is safely removed from the lungs in the average case It is only when a combination of adverse factors occurs—for example, the presence of a more viscid particle of tubercle-containing sputum, arriving at a bronchial junction where there is a high negative pressure in the adjacent bronchi—that dissemination takes place The surprising feature is not that bronchogenic tuberculosis occurs, but that it does not occur constantly when there is tuberculous material in the bronchial system.

Haematogenous or bronchogenic origin of post-primary lesions

Whether the usual initial post-primary clinical lesion—the subclavicular infiltrate, which is commonly situated anatomically in the posterior segment of the upper lobe, or less frequently in the apical segment of the lower lobe—is most frequently of haematogenous or bronchogenic origin is unproved Both methods undoubtedly occur, but the feature common to both sites, that they become the dependent area during recumbency, is very suggestive that the bronchogenic is the common source

If this hypothesis is correct, the initial post-primary clinical lesion fits in with the three usual methods by which relapse takes place

(1) The lesion, which has previously become quiescent or even appreciably healed, again becomes locally progressive

(2) There is bronchogenic spread from a bacilliferous unhealed focus into new areas, either detectable or not

(3) New foci appear, as the result of the reactivation of foci, usually bronchogenic, which were too small to have been detectable

These events happen quickly, especially bronchogenic spreads, this is the explanation of the cardinal feature of chronic pulmonary tuberculosis—that downward progress is mainly by sudden exacerbation of the disease, whereas retrogression is a slow and gradual process (Mayer and Piness, 1942)

ONSET OF DISEASE

The original discovery

Chronic pulmonary tuberculosis may become manifest in any of three main ways.

(1) Radiological discovery of pulmonary shadows

The discovery may be made radiologically of shadows in the lungs, which subsequent investigations prove to be due to pre-clinical tuberculosis. It is rare to discover abnormal physical signs in the lungs, caused by tuberculosis, which careful questioning does not prove to have given rise to some symptoms, though they may have been so slight that the patient has considered them to be unimportant.

Radiological examination of unselected groups of individuals indicate that in England about 0 6 per cent of individuals show abnormal shadows in the lungs, which are probably due to tuberculosis (Wingfield, 1936). Undoubtedly, if the structures producing them were subjected to full pathological examination, viable tubercle bacilli would be isolated in a high percentage of cases. The majority of the shadows are associated with absence of symptoms of any kind, and a subsequent follow-up shows that they remain unaltered when examined by serial radiography. On the other hand some of the shadows are associated with symptoms and other evidence of an unstabilized condition. There remain, however, a proportion of cases in which the radiological shadows lack the characteristics of completed stabilization but which are unassociated with symptoms or other evidence of lack of stabilization.

Discussion of the radiological characteristics of stabilization is dealt with in a subsequent section (*see* page 316), but it must be emphasized that, excluding fibrotic strands and calcified foci, an unequivocal opinion that only healed disease exists cannot be made on the evidence of a single radiograph. The term, "latent", is well applied to these shadows; for they include shadows which, although they have not the full characteristics, are subsequently proved to be due to healed disease, and other shadows which indicate disease which will become progressive or retrogressive, according to the result of the interaction of many factors. The appearance of any x-ray shadow indicating post-primary tuberculosis within 6–9 months of Mantoux conversion is usually of importance, and should always be treated seriously.

(2) The appearance of symptoms indicating toxaemia

The appearance of such symptoms is due to the production and absorption of material elaborated by the interaction of the bacilli and the tissues. Obviously, the toxaemia may appear within a matter of hours or days after the implantation of a post-primary focus, or within a period of weeks in a primary lesion, but whether this does or does not occur depends on the character of the host–invader clash. Many lesions of considerable magnitude are atoxaemic.

(3) The appearance of symptoms attributable to the local effects of the lesion

This means usually that the lesion has reached the bronchus, but secondary effects, produced by pressure on the adjacent bronchi, give rise to similar symptoms. In many cases symptoms of this kind are due to the mechanical effects (and subsequent secondary infection) of the changes produced by healing. Accordingly, toxaemic symptoms due to tuberculosis always indicate unstabilized disease. This does not hold for local symptoms.

Toxaemic symptoms

Toxaemic symptoms may be either obvious or so slight that the patient is unaware of them unless they are brought to light by careful questioning The most important line of exploration is comparison between the patient's state at the time of interrogation and, say, 12 months previously Most of the common toxaemic symptoms, such as excessive fatigue, malaise, loss of weight, loss of appetite, indigestion, irritability, and dyspnoea on exertion, are also produced by the strain of modern life, especially in young women who are working hard, playing hard, or keeping late nights, or who are in conflict with their environment Even if of pathological origin, they are, of course, not confined to tuberculosis, but may be due to other causes, such as chronic tonsillitis, anaemia, hyperthyroidism and so forth

The main distinction between symptoms of tuberculous toxaemia and stress symptoms lies in the fact that the former are found to have arisen within a period of a few months, during a time when other stresses have not increased In young people, toxaemia due to tuberculosis will usually steadily increase over a period of weeks or months within less than a year, if the toxaemia has existed without change over a long period, other causes are more likely A more chronic form of toxic symptoms often occurs in somewhat older patients It occurs in fibroid types of pulmonary tuberculosis when a considerable area of the lung is involved In these cases the patient will be found to be living a life of slightly subnormal activity, which he has found to be within his capabilities. A large number of cases of this type came to light at the beginning of World War II, the individuals concerned either undertook extra work in their businesses, or, under the spur of patriotic feeling, became Home Guards, Special Constables and so forth, by which means they sacrificed leisure which had enabled them to remain on terms with their unrecognized disease

Temperature

In the assessment of occult toxaemia, accurate temperature and pulse charts and observation of the erythrocyte sedimentation rate are essential Temperature records are useful onl [illegible]

will be adequate to take the temperature before rising, and at about 6 0 p m, after the patient has rested for 15–20 minutes In cases of difficulty the evening temperature should be taken for a week at 2 0 p m, 4 0 p m, 6 0 p m, and 8 0 p m, and the highest recording of these is taken as the evening temperature It is seldom that an individual knows his personal normal temperature but, if he does, it is of considerable value In the case of an average male, from 97 8°–98 2° F is a commoner normal temperature than the traditional 98 4° F in the mouth The [illegible]
higher A diurnal variati [illegible]
slightly raised evening tem [illegible]
of much greater significance than are isolated readings Many women have a

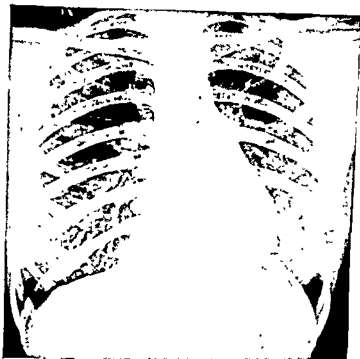


FIG 123.—Three years history of indigestion for which no cause was found Symmetrical fibrotic disease of both upper zones often connected with this symptomatology

premenstrual rise of temperature and this should be allowed for, but it is frequently exaggerated in pulmonary tuberculosis.

Amenorrhoea and gastric symptoms

Two special features may be mentioned Amenorrhoea is common in young women with tuberculosis—so much so that, if it occurs in a girl previously regular in her habits and pregnancy is excluded, a radiograph of the lungs should be taken In a proportion of cases with symptoms suggesting a gastric ulcer, a radiograph will reveal a shadow suggestive of pulmonary tuberculosis (Fig 123); often these shadows are of the fibrotic type, involving both apices fairly symmetrically.

Pulse

A raised pulse rate is present frequently in toxaemic cases Indeed, it sometimes persists when other evidence of toxaemia has abated. It is of little *help unless the patient is in an institution, or at least in bed at home* *The normal* rate varies within wide limits and emotional factors often render it unstable: but a persistently high rate, occurring in a patient when in bed, is presumptive evidence of toxaemia.

Psychological symptoms of toxaemia

It is mentioned above that irritability, in a previously even-tempered individual, is often evidence of tuberculous toxaemia. It was remarked by the nurses

working with one physician that, whereas previously he had been easy to please, during the month before pulmonary tuberculosis was diagnosed, nothing which they could do seemed right During recent years, much interest has been taken in the psychological make-up of tuberculous patients It has been suggested that certain types are more likely to fall victims to the disease This, it was claimed, was supported by the relatively high incidence rate of tuberculosis in mental institutions It is pretty certain, however, that this incidence is due to the low standard of personal hygiene of the patients, to conditions of crowding, and to the low general resistance of many of the patients

Wittkower (1949) has published a valuable monograph on the subject. Although as he readily admits that his conclusions are weakened by the absence of controls, he could find little evidence that any particular psychological type was unusually common among the tuberculous patients whom he studied He found that the strain produced by the diagnosis of the disease and by the length of treatment brought to the surface many latent abnormalities of personality

Local symptoms

Unlike toxaemic symptoms, local symptoms are as often caused by the after-results of pulmonary tuberculosis as by the tuberculosis itself, the tuberculosis may have become non-progressive or even be healed, but the symptoms may persist

Haemoptysis

Haemoptysis is, of course, the traditional symptom associated with pulmonary tuberculosis, and it occurs at some time or other in about 30 per cent of cases It is produced in several ways (1) From an early infiltration here the haemoptysis arises from congestion in the lesion and takes the form of streaking of the sputum or of small clots (2) From a cavity this is the cause of large-scale haemoptysis, which may prove fatal, and is probably due to the erosion of an unsupported vessel (3) From ulcers, or from granulation in tuberculous tracheo-bronchitis (4) A small haemoptysis is often the first definite indication that an exacerbation of a focus has occurred in a patient whose tissues are in a high degree of sensitivity The recognition of this fact is important, because at this stage the focus is susceptible to treatment with streptomycin (5) From tuberculous bronchiectasis It has become increasingly realized that tuberculosis is the cause of much bronchiectasis, and that upper-lobe bronchiectasis is seldom due to any other cause Of course, the tuberculous basis may have been merely mechanical, as when a gland of the primary complex, which has healed, subsequently produces partial occlusion of the bronchus

Failure to insist on adequate radiological investigation in a case of haemoptysis is culpable negligence Definite evidence of tuberculosis will be found in about 33 per cent of the cases.

Among the other commoner causes of haemoptysis are mitral stenosis, neoplasm of the lung, and bronchiectasis of non-tuberculous origin Slight staining may arise from acute tracheo-bronchitis or from bleeding gums, the characteristic feature of the latter bleeding is that it appears first thing in the morning and is frequently repeated Frequently repeated staining is seldom due to active

tuberculosis Even after the fullest investigation, there remains a group of cases *for which no cause can be found I have had* the opportunity of seeing all the members of the City of London Police who complained of haemoptysis, however slight, over a period of 20 years When no cause was discovered the men returned to duty, but they were regularly re-examined with x-rays for periods ranging from 3 to 5 years In 2 cases obvious shadows developed attributable to tuberculosis, re-scrutiny of the early films showed them to be extensions of pre-existing shadows which had been masked by the ribs In 3 of the remaining 30 cases small dense foci developed, which probably indicated tiny tuberculous lesions, but in the remainder *no cause was found Many of the 30 men, however, probably had* similar lesions, which were too small to leave a residual shadow. Unfortunately, Mantoux tests were not performed

Cough

In large towns in Great Britain, a cough in an adult is such a common symptom that little notice is paid to it In these days, when smoking is so common, a slight pharyngitis is not unusual, but patients are quite willing to put down a cough to the smoking of half a dozen cigarettes a day Others differentiate between " coughing " and " clearing of the throat ", and the questioning should specifically include the latter Complete absence of cough is not very common in bronchogenic tuberculosis, *though it does occur.* In pulmonary tuberculosis the cough has no diagnostic features, but some are suggestive In the early stages, the cough is often of the emetic character at the time of rising, quite out *of proportion to its severity , whenever tuberculous tracheo-bronchitis is present,* the cough has a spasmodic quality, and in fibroid tuberculosis a harsh dry type is common.

As with other common symptoms, it is the appearance of a cough which persists, or any increase of persisting cough without obvious cause, which is the important feature of the symptom

Catarrhal nasal pharyngitis is one of the common causes of cough, but a diagnosis of this does not exclude tuberculosis It has been noted by a number *of laryngologists that a persistent post-nasal catarrh is not uncommonly associated* with early pulmonary tuberculosis Whether this is a reflex phenomena is undecided

Sputum

The absence of manifest sputum is by no means uncommon in pulmonary tuberculosis, *but actually the absence of any bronchial secretions* which reach the larynx is unusual, except with the smallest lesion and in haematogenous [illegible] It has been claimed that if every possible method of examination of [illegible]

[illegible] sanatorium population was as high as [illegible]

Some patients, especially children, find it impossible to [illegible]

has arrived at the larynx into the mouth, and others, especially women, have taught themselves not to do so.

In active pulmonary tuberculosis the production of large quantities of sputum is usually associated with the presence of fair-sized cavities with thick walls, or else with tuberculous tracheo-bronchitis.

Chest pain

Pain in the chest in pulmonary tuberculosis is usually due to involvement of the pleura. In acute pleurisy the pain may be severe, but usually in parenchymal disease it is more of a dull ache. A spontaneous pneumothorax often produces a sharp pain at its onset; this, if due to tuberculosis, should be regarded as indicating active disease in the pulmonary parenchyma.

Whenever there is thickening of the pleura, or when a pleural effusion is the cause, a feeling of discomfort is more usually felt than actual pain. Occasionally a deep-seated ache is complained of over a sub-apical lesion, and questioning will often elicit this information even if the pain is not complained of.

Dyspnoea

This is commonly produced by mechanical causes, but it may be present on exertion in the early stages of the disease as a toxic phenomenon or one of presumably reflex origin. Dyspnoea occurs acutely with rapidly forming pleural effusion and spontaneous pneumothorax. Its severity varies rather with the rapidity of onset of these conditions than with their magnitude. In a more chronic form the following are common causes:

(1) Fibrosis and collapse of the lung, producing marked mediastinal displacement.

(2) Lack of function of the lung, due to miliary tuberculosis, extensive lung destruction, and emphysema following the healing of lesions, especially if these are widely disseminated. Its severity cannot be correlated with the radiographic appearances, owing to the inefficiency of the latter in the diagnosis of diffuse emphysema (Christie, 1934). Dyspnoea is of little value as a symptom in diagnosis, but very important in consideration of treatment.

Wheezing

This is an uncommon symptom and usually unilateral. It occurs in tuberculous tracheo-bronchitis, is inconstant, and is frequently noticed only when the patient is in bed. Its importance lies in its common attribution to asthma.

Physical signs

Value and limitations

In the presence of radiography, physical examination, as a method of diagnosis of tuberculosis of the pulmonary parenchyma is obsolete.

It has been said *ad nauseam*, but it must be repeated, that failure to find abnormal physical signs in the chest, even by an expert, does not exclude the existence of pulmonary tuberculosis, any more than it does, say, a hammer-toe in the foot, for in one case the hammer-toe is hidden by the shoe, in the other the lesion is hidden by the tissue around it.

This does not mean that physical examination is valueless, for, although adequate radiology reveals all that physical examination can tell and much

In the male adult, the absence of vocal fremitus assists in the differential diagnosis between a pleural effusion and a pneumothorax, and a feeling of resistance is characteristic of a large effusion

Percussion

[illegible]

finger is not marked by intervening lung tissue. A fairly confident diagnosis of fluid in the pleura can often be made, and the best place in which to put the exploring needle can often be discovered when the information from a standard x-ray film is equivocal Small areas of localized emphysema diminish the value of percussion in many cases.

Auscultation

Breath sounds —The method by which the breath sounds are normally produced [illegible]

the pleural membranes None of these processes is peculiar to tuberculosis. It is only the predilection of tuberculosis, as compared with other infections, for the upper zones of the lungs, which renders their discovery in any way diagnostic of tuberculosis. Hence the value of auscultation lies in the elucidation of pathological conditions which are compatible with tuberculosis, and are most likely to be caused by this infection, owing to their position and distribution. In most cases an x-ray picture is a more accurate guide but, in the diagnosis of pathological changes below the diaphragm level and behind the heart, the character and relative intensity of the breath sounds may be most helpful.

Additional sounds —Added sounds are in a different category. Apart from bronchography, the x-ray picture, even aided by careful screening, tells us little about what is happening in the bronchial tubes, although obstruction may be deduced and, by tomography, even demonstrated The modern conception is that all forms of râles are produced by moisture Because the production of moisture in localized groups of bronchi, in the upper zones, is most commonly [illegible]

below the clavicle, anteriorly

[illegible] g of [illegible] icky [illegible] the

bronchi are localized, so generalized sounds of this kind are not characteristic of tuberculosis Localized wheezing and rhonchi are suggestive of tuberculous tracheo-bronchitis Wheezing heard at the open mouth (Chevalier Jackson's sign) is a useful confirmation of the obstruction

Râles —The value of râles as evidence of activity of the lesion is not as great as is often thought The elicitation of fine localized râles can be considered as presumptive evidence that the lesion is unhealed, but it must receive confirmation by other methods In a case of pulmonary tuberculosis, however, the finding of localized râles, in an area in which previously there was no evidence of disease, must be [illegible]ed as suggesting a spread of the disease, and therefore as evidence of activi[illegible] pleurisy [illegible]

Pleural friction —[illegible] though screening often shows diminution [illegible] friction, therefore, will lead to a diagnosis of acute pleurisy in the absence of radiological evidence, but unfortunately pleurisy often occurs in the absence of friction

THE INCIPIENT BRONCHOGENIC LESION

Definitions

Much confusion has been caused by the lax use of descriptive terms The terms, early, incipient and minimal tuberculosis, have been used by many writers as more or less synonymous This is obviously incorrect. "Early" must refer to time ; thus it can equally correctly be used to describe acute pneumonic tuberculosis and a lesion so small as to be hardly radiologically detectable; but the former cannot be described as minimal whereas it is a correct description of the latter "Minimal" refers to the extent of the disease and has nothing to do with time. Properly used, the term, incipient, has the same meaning as "early", but it is seldom applied to an extensive lesion It is clear, therefore, that within its limitations—a single shadow of slight density of less than 0 5 centimetre can hardly be definitely diagnosed—a single x-ray picture will determine whether or not a lesion is minimal, but is by no means infallible in deciding whether or not it is early. Only comparison with a previous normal film will determine this.

When the lesion is established, the rate of progression is variable. In a few months, serial films taken of students' lungs may show successively a normal film, a minimal lesion and an extensive lesion in one case, and a normal film, a doubtful lesion and an equally slight lesion in another

In the United States of America it has been shown that, in-patients who were found on re-examination after 1 year to have developed pulmonary tuberculosis, advanced disease was present in Negroes 3 times as frequently as in white patients.

Radiological characteristics

The study of incipient lesions has been recently much clarified in a paper by Reisner (1948) He confirms and amplifies previous papers by Amberson (1942) and Brauening (1938) His figures are based on 250 cases (20 per cent Negro and 80 per cent white patients) The material consisted of contacts of cases of pulmonary tuberculosis, who had had a normal film x-ray, but in whom shadows, diagnosed as tuberculous, appeared within 12 months, with an average of 7 months Tuberculin tests were available in only a small proportion, but were nearly all positive when done, and the degree of contact made it unlikely that many cases of primary lesions were included Even in this and other similar series, a caveat must be entered It can be agreed that they were

radiologically early, but they may have been exacerbations of lesions which were previously too small to be radiologically detectable Theoretically, all cases should have been recently Mantoux-negative, and should have a primary complex and a subsequent post-primary lesion

Radiologically, the incipient lesion may be of several types (Figs 124 and 125):

(1) a soft, ill-defined shadow—the smudge type;

(2) a cluster of more definite nodules;

(3) a round dense shadow, with well-defined edges;

(4) an area of confluent lobular or massive pneumonia.

These types are comparable with Reisner's classification

Reisner (1948) points out that accurate classification is not easy. Subject to this reservation, he found that the frequency of occurrence was as follows: 50 per cent were of the smudge type, 7 per cent nodular, and 11 per cent showed both these types, 7 per cent showed round circumscribed, and 25 per cent pneumonic shadows in which cavities were common Of the minimal cases about 75 per cent were of the smudge type. The relatively high proportion of cases of the pneumonic type was due to inclusion of 60 Negro patients, in whom it was four times as common as in white patients

Position of the lesion

It used to be held that the early lesion first appeared at the apex and spread downwards Jaches and Wessler (1923) pointed out that early shadows did appear in the subclavicular region, but to Assman (1927) belongs the credit for pointing out that the subclavicular region was the common situation His work was on cases with early symptoms, and the shadows he described were frequently quite large These subclavicular shadows he called the "early infiltrate" (Figs 126–131). Unfortunately, he and his followers thought that the apical shadows were of little *clinical significance, which subsequently was proved to be incorrect*

The situation of the shadows is in the first or second interspace, usually towards the periphery, and is actually in the posterior part of the subapical segment

In Reisner's series of 220 minimal early lesions, 20 per cent were supraclavicular, 55 per cent were subclavicular, 15 per cent showed lesions in both these situations, and 8 per cent showed lesions in the mid-zone, probably mainly in the apical segment of the lower lobe (Reisner, 1948)

A similar proportion was found in the Prophit Tuberculosis Survey (1948d) when dealing with 91 cases considered to be "early".

Unfortunately, these radiological appearances seldom can be correlated with the pathological conditions producing them, because post-mortem evidence can only be obtained by rare accident Hence the relationship between the

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From the limited post-mortem material available, it would seem that there are many incipient lesions in both the apical and subapical areas, which radiology does not reveal

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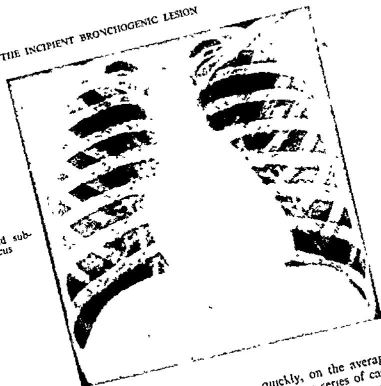
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FIG 124 —Subclavicular nodular early infiltrate.



—Round sub-
...cular focus

Extent of lesions

It is only by chance that it is possible to say how quickly, on the average, incipient lesions develop It is impracticable to re-examine large series of cases radiographically more frequently than every 12 months, and even contacts can seldom be re-examined oftener than every 6 months Reisner (1948) found, in his series of early cases, that 75 per cent of the lesions were minimal in white patients and 50 per cent in Negroes

All experienced observers have seen cases in which a shadow has appeared within a few weeks or months I have seen a subclavicular shadow appear and disappear within 10 days in a case with a tuberculous pleural effusion, but the effusion may have masked a previous lesion, although there was no evidence of its presence when the effusion cleared

Symptoms

Neither the age of the lesion nor its extent go *pari passu* with the presence or absence of symptoms

Incipient lesions are discovered by x-ray films, but some of the patients, of course, have symptoms The extremely gradual onset and indefinite character of the symptoms often makes it difficult to say what proportion of the early cases are really asymptomatic Even the most careful questioning at the time of diagnosis often will not produce a history of mild toxaemia in a case in which, after a month or two in bed, the patient volunteers the information that he is now feeling much better and had not realized previously that he had been tired.



FIG 126.—Subclavicular early infiltrate, "smudge" type Skiagram taken 6 months previously showed no abnormality.

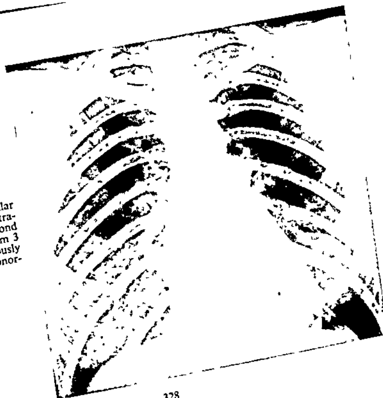


FIG 127.—Nodular type early infiltration, left second space Skiagram 3 months previously showed no abnormality

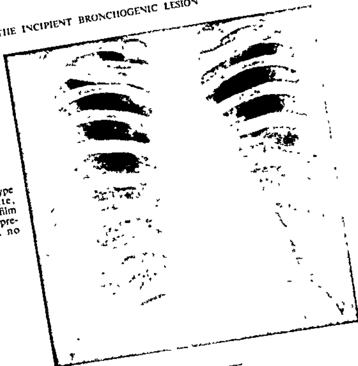


FIG 128 —Nodular type of early infiltrate, supraclavicular A film taken 1 year previously showed no abnormality

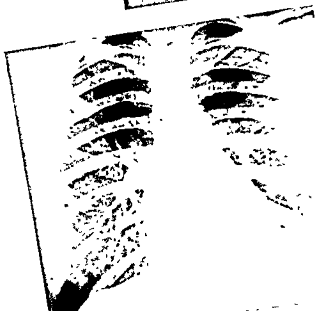


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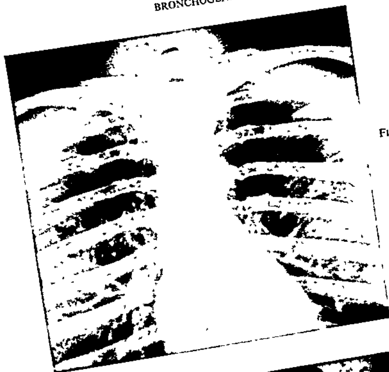


FIG. 130.—Supraclavicular infiltrate, nodular type. Skiagram taken 6 months previously showed no abnormality.

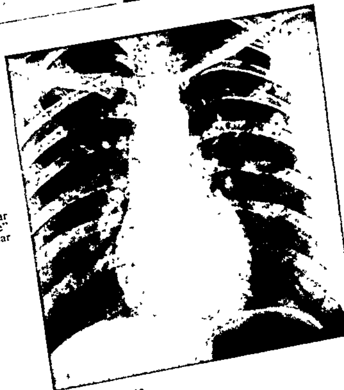


FIG. 13 .—Subclavicular infiltrate, "smudge" type, normal 1 year previously.

Reisner found that, in patients with minimal disease processes only 20 per cent admitted to any symptoms Abeles and Pinner (1941) and Bobrowitz and Dworke (1946) found that most of their patients had had some symptoms ; both these papers, however, dealt with patients in sanatoria, who had had plenty of time to think about themselves

It seems probable that comparatively few minimal early lesions will cause symptoms which would give the normal individual the slightest anxiety, and thus send him to his doctor.

ORIGIN OF THE INCIPIENT LESION

The original infection, the primary lesion, is now fairly well understood In recent years the early lung lesions have been studied extensively, with the result that it is possible to give a reasonably clear radiological description of them They represent the beginning of the common form of progressive pulmonary tuberculosis, called the " adult type ", post-primary type, or " phthisis ", and the spread is largely bronchogenic It differs from the primary lesion in that there is little glandular enlargement, and that, if there is enlargement, there is, as Pagel (1948a) has emphasized, comparatively little caseation

Basically this form is the lung reaction in the immunized individual, and its localization to the lung is evidence of resistance, both natural and acquired ; but between the primary lesion and the incipient lesion there is a stage in which theory wanders freely, hardly guided by established fact

It has been held that, if an infected individual reaches 30 years of age with a normal x-ray film, it is unlikely that he will acquire pulmonary tuberculosis. Reisner's figures do not support this contention He found that about 16 per cent of his patients who were diagnosed as having early tuberculosis were over 30 years of age , his cases were not, however, an average sample of the average age-groups of the population.

Other observers confirm that, at any rate, the percentage of cases of early lesions in middle-aged patients is by no means negligible Whether or not this is connected with the postponement of primary infection till adult life, which is occurring in the United States of America, is not settled

On the other hand it must be emphasized that this finding does not apply to minimal tuberculosis leading to active disease

Chang (1948) has studied 164 cases of minimal disease seen in a sanatorium The proportion of patients who were found to have active disease was twice as great in those under 38 years of age as in older age-groups. A considerable proportion of cases classified as " active " in the over-38 group were put into the category only as the result of the recovery of tubercle bacilli from sputum and gastric-lavage contents, confirmed by cultures or guinea-pig inoculation ; no other evidence of activity was discovered

Methods of production

There are three possible methods by which bronchogenic tuberculosis may be started (1) endogenous exacerbation, (2) exogenous superinfection, and (3) exogenous reinfection.

Exogenous reinfection

Exogenous reinfection may be dismissed briefly. The term implies that the previous infection has healed to such an extent that no living tubercle bacilli remain, and hence that the body is no longer allergic to the tubercle bacillus, as shown by the re-conversion of the Mantoux reaction to negative In fact, there is again virgin soil, although this latter statement is not quite correct; there is some evidence that acquired immunity is produced more quickly by the reinfection than by the initial infection. A new primary infection is produced, which behaves in the same way as the original infection Any bronchogenic tuberculosis which may result will be produced in the same way as it was by the primary infection and its endogenous exacerbation

Both from the clinical and the pathological point of view it is impossible to differentiate between this and the other methods of production of bronchogenic disease, and its epidemiological implications are similar. Its occurrence seems to be variable.

Lloyd and MacPherson (1933) found about 3 per cent of reconversion in 300 healthy children attending for 2 years at Brompton Hospital, but (according to a personal communication by MacPherson) recently the percentage has been lower In the United States, however, papers have been published showing a reconversion rate of over 2–3 per cent per annum, and over 10 per cent in varying periods (Rich, 1944b) In the Prophit Tuberculosis Survey (1948b) it was found that 5 per cent of the non-contacts (students and nurses) reconverted within 1 year, whereas re-conversion only occurred in 1 5 per cent of contact cases. As yet no investigation has been published which shows the effect of reinfection on these re-converted cases

Although the distinction between reinfection and superinfection is important *theoretically*, *practically* it is not so The chance that the lungs of a patient
... proved by radiological evidence,
... t is not helpful—
... *reinfection*, *must*
be used to cover exogenous superinfection; this is done by many authors. In the present section the term, exogenous superinfection, is used to cover possible reinfection lesions which are not proved to be *reinfections*

Exogenous superinfection

... *has been hotly debated. Un-*
...d
...ly
... received by human subjects. The protagonists of exogenous superinfec... ...n
... ...ho have received a primary
... a larger number
... case in contact
with them Again, there is nearly universal agreement that children who have received a primary infection *are less likely to* develop progressive tuberculosis if they are removed from *further* contact with an *infectious* case. It has been claimed that, because a long interval *often occurs* between the primary infection (which, indeed, sometimes results in an *apparently pathologically* sterile focus)

and the onset of progressive tuberculosis, exogenous superinfection is likely to be a common cause of the latter. The argument seems fallacious because, if the Mantoux reaction is positive, living tubercle bacilli must still be present in the body, and, even if the primary focus and gland do not contain living bacilli, there may be plenty in daughter foci elsewhere.

Malmros and Hedvall (1940) point out that, out of 79 primarily infected medical students and nurses, 22 per cent developed post-primary lesions, but that out of 72 similarly infected non-medical students only 3 per cent developed post-primary lesions

Similar results are recorded by Madsen, Holm and Jansen (1942)

The authors of the Prophit Tuberculosis Survey (1948c) point out that the proportion of re-conversion of the Mantoux reaction is much higher in subjects who are not known to be subsequently exposed to infection This indicates, at any rate, that tubercle bacilli are deposited in the body subsequent to the primary focus, and that they do, at all events, have a definite effect in producing an allergic condition This finding provides an answer to the contentions of Lange (1934)

The work of Lange, who contended that the size of the bronchioles precluded the likelihood that a significant number of tubercle bacilli would reach them, has often been quoted against the importance of exogenous superinfection

Rich (1944) has also pointed out that Lange has underestimated the number of bacilli which can be carried by a particle of sputum small enough to penetrate to the terminal bronchiole This is of great importance, for the number which settle at one point influences the rate of propagation in a susceptible animal Morbid anatomists, especially Paget (1935), have produced much material against the theory of superinfection but Paget himself has found that small doses of bacilli, repeated at short intervals, have an important effect The level of resistance in the normal individual varies from time to time in a way not obvious in the animal experiments

Plunkett and Mikol (1940) reported that, in an institution for the feeble-minded, 1,059 patients were found to be Mantoux positive, but to be free from active pulmonary tuberculosis Of these, 826 were looked after in wards in which no open case of tuberculosis resided, but for administrative reasons the other 243 were treated in wards in which there were open cases During the subsequent 3 years no case of active tuberculosis occurred among the 826, whereas no less than 10 were found among the 248 patients who were in contact with open cases of tuberculosis

The balance of evidence seems to indicate that exogenous superinfection certainly does take place, but it fails to determine the extent of the part which it plays in the production of bronchogenic tuberculosis When the number of bacilli inhaled into the bronchi is large and the doses are very frequently repeated, this method is certainly important It is also possible that other favourable factors are necessary for example, that the normal resistance is, for some reason, temporarily depressed With so much doubt as to the importance of endogenous and apical infection, it is futile to speculate on the exact train of events by which the incipient lesion develops from this cause After bronchogenic tuberculosis

has developed and tubercle bacilli are normally present in the bronchi, it is difficult to think that a few more or less will normally have any effect.

Endogenous exacerbation

There are a number of ways by which a primary infection may lead to the *incipient lesion of* bronchogenic tuberculosis, but they must fall under two headings

(1) The direct effect of the *primary lesion* this need not be immediate the primary lesion may remain latent, with tubercle bacilli in both the lung and gland component for many years.

(2) The effect of post-primary lesions, produced by the primary lesion during the time of its activity.

Effect of the primary lesion

The importance of the direct effect *of the primary lesion has been emphasized* during recent years. Scandinavian authors and, more recently, Swiss authorities have produced incontrovertible evidence that, in young adults at any rate, progressive primary tuberculosis does occur Reading the literature, it is very difficult to reconcile the reports of its importance by the highest authorities in Scandinavia *with those* by equally reputable workers in the United States and Great Britain

The subject is dealt with more fully in the section on "primary tuberculosis". It is difficult to avoid the conclusion that the percentage of cases in which the disease commonly takes one form or another is different in different countries, presumably as the result of variation of native resistance or in the age at which primary infection commonly takes place

If bronchogenic tuberculosis arises as the direct effect of the primary lesion, it may do so either (i) from a recent primary lesion or (ii) from a primary lesion which has healed incompletely but in which reactivity has taken place at a later date

Around the primary lung focus small areas of infiltration are sometimes found. These are adjacent to, but not part of, the primary focus; *presumably these* areas are produced by lymphatic (or possibly by bronchogenic) spread. Apart from a possible bearing on progressive primary tuberculosis, it is unlikely that they play an important part in producing bronchogenic tuberculosis. It is claimed that there is no predilection by the primary focus, for localization in the upper zone of the lung, which is characteristic of bronchogenic lesions (Fig *132*)

In cases in which disseminated lesions in other parts of the body are found *immediately following the primary lesion, other* lesions have been found in the lungs which are not part of the primary focus They probably come from the Paget (*1935*) *has pro-*

njected into guinea-pigs,

tubercle bacilli can be obtained in about 20 per cent of these *apparently healed* lesions That glandular lesions can become reactivated is undoubted *It is* well known that glands may break down and produce progressive disease by discharging their contents through the bronchial wall, especially in *old* age. *A*

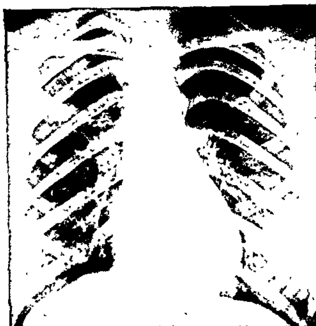


Fig. 132 — Primary focus in a young woman Mantoux negative in May 1949, positive August 1949 Erythema nodosum July 1949 at the time when this film was taken

typical example is a girl aged 22 years who had an acute tuberculous effusion. This subsided under treatment. After treatment she remained perfectly well for some years, with a radiograph which showed no abnormality except slight pleural thickening She then began to suffer from a cough and unilateral wheezing Bronchoscopy showed a gland which was being extruded into the bronchus. When under treatment for this condition she developed a bone lesion

However, the commonest method of spread from this source must be by haematogenous dissemination into the lung The recrudesence of an apparently healed primary pulmonary focus is by no means so clearly proved, but it certainly may occur in exceptional circumstances In a girl aged 18 years, a typical lung abscess developed following tonsillectomy A little later, tubercle bacilli were found in the sputum Re-scrutiny of an early film showed that in this area there was an undoubted primary focus Later films showed that the calcified area had disappeared.

The effect of post-primary lesions

There is plenty of evidence that, during the time of activity of the primary complex, dissemination may take place into the lungs This is normally produced

the lesions by their appearance occasionally in batches and by their existence in such other organs as the spleen When these post-primary deposits occur in

the lungs they are found most frequently in the upper zone. They usually heal and become invisible radiologically, but in an appreciable percentage of cases living tubercle bacilli may be recovered from them

There are at least three types of post-primary deposits.

(1) *Pleural caps and apical scars.*—In many individuals areas of apparent pleural thickening can be demonstrated radiologically and pathologically. These are often associated with fibrotic scars underlying them. In some there is undoubted evidence of tuberculous lesions, usually calcified and healed. If these are present the tuberculous origin of the pleural cap is undoubted In others the tuberculous aetiology is not proved pathologically and they may be due to non-specific fibrosis. But some of these caps may still be tuberculous, for some tuberculous lesions heal so completely that the characteristic picture of tuberculosis disappears This is well shown in chronic haematogenous dissemination in children, in which foci in all stages of healing may occur; in some of these foci there is no pathological proof of their tuberculous origin, whereas on clinical grounds the origin is undoubted

The healing in pleural caps and apical scars is so sound that there is little evidence that this factor plays much part in the production of the incipient lesion

(2) *Small encapsulated caseations.*—There are often small encapsulated caseous areas In children they frequently calcify (Simon's foci), but they may often be shown to contain tubercle bacilli

(3) *Large encapsulated foci*—In other cases much larger foci are found They are encapsulated and contain caseous material, and tubercle bacilli are often present.

Possible effects of disseminated lesions

There are two possible effects which may result from these disseminated lesions if they are awakened from their latent state They can turn into active lesions and become manifest incipient foci of disease on their own; alternatively, they may break down and, while failing, owing to their small size, to produce radiographic evidence of change, they may discharge tuberculous material into a bronchus and give rise to sub-clavicular infiltration by bronchogenic spread.

The incipient lesion of bronchogenic tuberculosis may then possibly arise in a variety of ways, but which of these are the common methods it is impossible to say Pagel (1948b) has tried to do so on the basis of some 30 cases, in which, for one reason or another, autopsy was possible while the tuberculous lesions were apparently in the early stages, but, as he points out, it is unjustifiable to draw very definite conclusions He does seem to show that, apart from cases which followed a progressive primary lesion, the exacerbation and direct progression of a post-primary lesion, or of a bronchogenic seeding from a similar small focus, are common methods by which the incipient lesion of bronchogenic tuberculosis develops

DEVELOPMENT OF THE INCIPIENT LESION

The minimal lesion

The process of development is best studied in the minimal lesion.

In the diagnostic standards of the National Tuberculosis Association of the

United States of America, "minimal tuberculosis" is defined as slight infiltration without demonstrable cavitation, the total volume of which shall not exceed the equivalent of lung tissue which lies above the second chondro-sternal junction and the body of the fifth thoracic vertebra on one side.

This definition includes primary and post-primary lesions. An important paper by Medlar (1943) based on over 1,000 autopsies, discussed these with relation to the primary complex. He shows that, whereas in children the primary focus may appear anywhere in the lungs, in adults the primary lesion occurs in the upper zone in a high proportion of cases. His work is open to objection, for he assumes that, because he could not, after the most careful investigation, find any evidence of tuberculosis elsewhere, the lesion was primary; reports on Mantoux tests were not available so the weight of evidence which he produces is diminished by this omission.

Medlow's work adds force to the contention that, unless a primary focus can be demonstrated, the radiological distinction between a primary and a small reinfected lesion is very difficult. Thus any series of minimal lesions must often include primary and post-primary lesions.

The radiological appearances of minimal lesions, according to the authors of the Prophit Tuberculosis Survey (1948d) who examined 154 cases, merged so much into each other that they felt that it would be misleading to give the respective percentage of nodular and smudge types; but the percentages of the various positions of the lesion were roughly the same in the minimal and the apparently early lesions. (The Prophit minimal cases were smaller in extent than the United States definition allows.)

Brooks' (1944) findings in the study of half a million apparently healthy naval personnel are very important. In all, 3,000 cases (0.5 per cent of the total) showing a minimal "adult type" of lesions were found, after full investigation, 16 per cent were considered to be active, 21 per cent to be of healed disease, and 63 per cent were doubtful. Of these doubtful cases in over 10 per cent activity had developed within 1 year; that is to say that nearly 25 per cent of the 3,000 cases showed frankly progressive disease within 1 year.

Modes of development

In the development of the early lesion when it is still minimal, there are three possibilities.

(1) *Progression*.—Progression of the disease may occur either rapidly with or [illegible] resolution [illegible] caseation has occurred. It is a commonplace finding that calcified spots may appear in areas where no evidence of disease has been visible in earlier films; hence complete radiological disappearance does not imply complete pathological resolution. Retrogression may also take place by fibrosis or calcification; usually there is a combination of the three. Only complete sterilization of the lesion precludes reactivation.

(3) *Stabilization*.—No change takes place, at any rate during the period of observation.

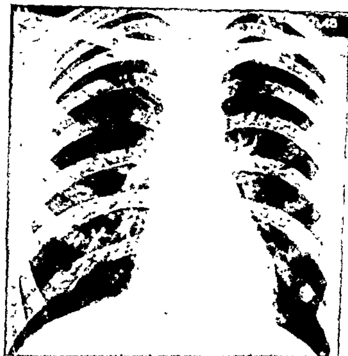


FIG 133—Subclavicular infiltrate with early cavitation Film 6 months previously showed no abnormality

Development and indications for treatment

Reisner (1948) found, *in periods of observation of minimal cases averaging* $3\frac{1}{2}$ years (minimum 1 year), that out of 206 white patients not treated by collapse or with antibiotics, 50 per cent of cases showed frank progression and 25 per cent slight progression , 28 per cent developed radiologically demonstrable cavitation No difference was observed between the different radiological appearances and anatomical situations. In 50 per cent of frankly progressive cases the progression took place within 2 years, but progression was still occurring in some cases at the end of 5 years, when the observation ceased. Retrogression in some degree took place in 20 per cent of cases, but in only half the number did this lead to eventual stabilization. No difference in the percentage of frankly progressive cases was apparent in patients over or under 25 years of age Reisner's conclusion is that the percentage of early minimal cases which stabilize themselves is too low to permit of anything but immediate adequate treatment. /

Similar results were found by the authors of the Prophit Tuberculosis Survey and of other investigations, except that they considered that frank progression took place more frequently in sub-clavicular than in apical lesions.

A reasonable conclusion is that most, if not all, early minimal cases require treatment In minimal cases in patients of doubtful age, definitely active cases must be treated, whereas in the remainder very careful observation is the happy medium between unnecessary treatment of many patients and undue optimism.

PROGRESS AFTER THE INCIPIENT PHASE

Every bronchogenic tuberculous lesion in the lungs is made up of one or more of the following pathological ingredients .

(1) Perifocal exudation, (2) caseation, (3) cavitation, (4) fibrosis, (5) tracheo-bronchitis of the draining bronchi

Factors affecting progress

On the proportion at any time of the ingredients depends the progress of the disease, but they need not and frequently do not remain constant , variations
be termed
ingredients ;
individual

This variation both of type and progress is difficult to understand, unless there is a local difference of hypersensitivity or unless chance factors permit multiplication of the bacilli at different rates and in different areas ; hence an increased concentration of bacilli may be present from time to time in any one area without a similar increase in another

The whole course of progress of the lesion is governed by the Koch phenomena. In the sensitized subject the area where the lesion exists is sacrificed, if necessary, in the interests of the whole body Around the tubercle bacilli an inflammatory reaction takes place, resulting in caseation and liquefaction ; a communication is then made to the exterior and the caseous material is extruded together with the main mass of tubercle bacilli

The first four of the six factors mentioned above are, of course, common to all tissues attacked by tuberculosis, and it is only necessary to discuss the clinical features peculiar to the lungs ; but the existence of bronchogenic spreads and bronchial tuberculosis produces special features which are peculiar to pulmonary tuberculosis

When the tuberculous material reaches the bronchi but fails to be evacuated, it is aspirated into a bronchial segment, which may or may not have been the seat of previous tuberculous inflammation (Figs 134–135) On the face of it, it would seem less likely that the aspiration takes place as easily into severely damaged areas, as it would into less damaged areas ; a functionally intact area would be more likely to aspirate such material, owing to its unimpaired elasticity but, on the other hand, the same factors would lead to a decrease in the probability of evacuation of the pus if it once became implanted This would not apply to markedly dilated bronchi , from these, Lipiodol is usually quickly cleared in bronchograms An attempt has been made by Young and Ganz (1941) to determine whether Lipiodol which had reached the alveoli was likely to remain in areas that had been the seat of previous damage, but the authors of the paper were unable to convince themselves that this was a fact

Any impairment of the scavenging action which keeps the bronchi clear is important in allowing spreads of disease ; *there is little doubt, for instance,* that after thoracoplasty there is a predilection for aspiration spread into areas which have been previously damaged An important factor is the concentration of bacilli in the aspirated material ; it is well known that a relatively benign result often follows aspiration of blood containing tubercle bacilli after

FIG 134—Bronchogenic spread into right middle lobe from apical cavity Right lower zone was apparently normal 3 months previously.

FIG 135—Tension cavity, left subclavicular region This appeared suddenly and was associated with a bronchogenic spread into the middle zone of the right side The cavity spontaneously disappeared, and the condition was similar to that 6 months earlier

haemorrhage from a cavity. Following such an aspiration there is often a brisk reaction, but if it is adequately treated, the clearing is often rapid and relatively complete as compared with an aspiration spread of sputum from a similar cavity. It can hardly be that the blood causes a non-specific broncho-pneumonia; the clearing is too slow for this; but presumably the concentration of bacilli per millilitre of blood is much less than in sputum, and each area of the lung can deal with numbers of bacilli which, if aggregated into one area, would be able to cause spreading disease.

The question of numbers must also play a considerable part in determining the occurrence of spread in a bacilliparous case. In any such case, bacilliparous sputum must be lying in the bronchi more or less constantly, yet in many cases no spread will take place for years; eventually, however, a spread does take place. It is almost inconceivable that the scavenging mechanism and resistance are so good that aspiration does not take place; if this supposition is accepted, it would seem that the most likely variable factor is the number of bacilli which are aspirated and concentrated in any one area. A less likely alternative is that bacilli are aspirated into areas of tissue with different or varying degrees of hypersensitivity, and therefore with different results.

The tuberculous bronchitic factor is difficult to estimate. A source of bacilli is provided, but the number must be small as compared with the number produced by large cavities. On the other hand, if stenosis is present the chance of aspiration into a comparatively unaffected area behind the block must be increased; presumably it will be more difficult for the bacilli to be evacuated. Another variable is that the oxygen concentration in the area behind the affected bronchus may be appreciably different as compared with the normal bronchus.

Consideration of the varying pathological possibilities which may exist at any one time and of the possibilities of variation, not only in the individual but also in different lesions in the same individual, makes it clear that it is unlikely that we shall ever be able to assess accurately the progress of the disease, lesion by lesion. It is, however, worth while discussing the features of certain types which illustrate the basic facts.

Bronchogenic tuberculosis in which caseation plays the prominent part

The effect of this is largely dependent on the extent of pulmonary involvement, but the extremes are (i) small nodular lesions and (ii) lobar caseous pneumonia. Radiologically, the former consists in ill-defined shadows of medium density and varying in individual size and number. The pneumonic type appears as a dense, more or less homogeneous shadow with a lobar distribution; clinically, there are few local symptoms and the toxic symptoms vary. Large areas tend to give rise to more toxic symptoms than do those which are small, but this distinction is by no means invariable.

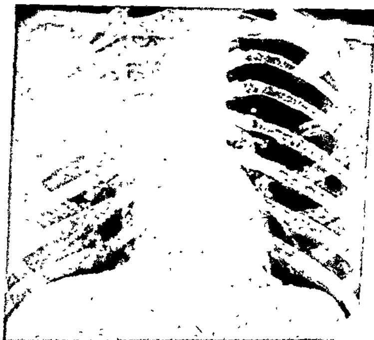
Lobar caseous pneumonia

Lobar caseous pneumonia which usually has an acute onset may settle down to a more chronic phase (Fig. 136). The signs are similar to those occurring in pneumococcal pneumonia, but the toxaemia is seldom so severe and, of course, rapid clearing does not take place. This form of the disease tends to occur in communities



FIG 136 —Caseous tuberculous pneumonia.

(a)



(b)

which have not had much contact with tuberculosis in earlier generations (for example, American Indians, or Negroes), and is commoner below the age of 30 years Pinner (1945) has used the expression "primitive" for these communities. In these cases the downward progress of the disease may be uninterrupted, and it may be fatal within 6 months or less—"galloping consumption". Extensive cavitation will develop if the progress is less rapid, but in typical cases the amount of sputum and number of tubercle bacilli are small

This, however, is not the invariable picture; in older patients, who have carried chronic tuberculosis more or less successfully for many years, this type of disease may be superadded The typical sequence is progressive cavitation in a diseased area and aspiration from this with lobar involvement; alternatively, in a similar type of case and in children, ulceration of a caseous gland through the bronchus gives rise to a similar pattern of disease In the old-age group the original, more or less non-progressive lesion presumably indicated a high resistance; thus the occurrence of tuberculous pneumonia, typical of a poor resistance, in the same individual illustrates the difficulty which confronts anyone in trying to explain the phenomenon of resistance

The prognosis of the pure type used to be bad, but newer methods of treatment have altered this, at least temporarily; though whether the resolution of disease which follows the use of streptomycin will produce a permanent effect is not yet known In older age-groups it does not seem likely that the resulting improvement will be more than temporary If clearing does take place, it must be the perifocal inflammation which clears away, for the caseated areas represent destroyed lung and must therefore be slowly replaced by fibrous tissue

In the younger individuals the permanent damage may be less, but unless the cause of the appearance of this type in the individual case is an overwhelming dose of bacilli, the usual basic factor, lack of resistance, seems likely to persist, and a bad prognosis remains likely

Caseous pneumonia with cavitation

If the caseous pneumonia is acute, little cavitation will take place because of the time factor, but if the patient survives long enough, excavation will take place. The fact that it does so indicates that the organism has been able to mobilize some defence In these circumstances the cavities are of the wall-less type—mere holes in the lung. The clinical picture now changes, the lung begins to get rid of the caseous material, hence the toxic symptoms tend to become less and the temperature falls At the same time the character of the latter tends to change, the sustained high temperature becomes replaced by a morning remission or intermission The sputum becomes much more plentiful and now contains tubercle bacilli in large numbers Unfortunately, however, the combination of large amounts of bacilliparous sputum and the lack of ability of lung resistance to deal with it, when aspirated into other areas, usually leads to bronchogenic spread. Occasionally, if sufficient material is discharged without spread, the defensive mechanism seems to pick up strength, if so the rapid breakdown of lung tissue is stayed; fibrous tissues begin to appear in the cavity walls and the lung lesion is replaced by dense fibrosis with cavities This leads to marked shrinkage The process may continue; in this type of disease tuberculous

bronchitis is common, and as fibrosis continues in the lung a simila occurs in the bronchi, bronchial occlusion, leading to cavity closure, place, but it is not often that the process is complete; a shrunken with thick-walled unhealed cavities is the most likely result.

Up to this stage collapse therapy, especially pneumothorax, is contra but if the favourable trend continues the next stage is produced. It is collapse therapy finds its real place.

Bronchogenic tuberculosis with fibrosis and cavitation

This is the common adult type of disease. As indicated above, it ma from pneumonic or caseous tuberculosis, but it usually follows on the early lesion The resistance of the patient and the invasive power of t are evenly matched, and the battle sways backwards and forward fortunes are in the patient's favour, few caseous areas break down and is slight, the patient may go on for many years with a positive sputu is examined), but with moderate health If things are less favoural cavitation takes place and bronchogenic spreads occur

The favourable type was well illustrated during World War II. A n middle-aged men who, because of sub-standard health, had drifted i jobs and instinctively led a quiet life outside business hours, were called work much harder because their colleagues were called up, and to u Home Guard and fire-watching duties This tipped the scales against t progressive tuberculosis followed In late middle age the body resistan to deteriorate and a latent lesion becomes progressive In these cases of tuberculous pneumonia are common. Owing to previous shrinkag lung and to the comparative slight degree of toxaemia, these areas a thought to be collapsed, but the pneumonial element is much greater a important than the collapse

The predilection of this type of disease for the upper zones and the fibrotic element lead to an apical migration of the diseased areas and a ponding compensatory emphysema in the lower zones The less heal are commonly below the more healed areas, which occupy the apices

A minor but interesting point is that the more symmetrical the dist of the radiological shadows, the better is the prognosis. This symmetric cavernous disease is not infrequently noticed by the radiologist when he is out routine screening, prior to examination with a bismuth meal, und for gastric symptoms

Fibro-caseous tuberculosis

and in many cases when normal resistance is lowered the ...



FIG 137 — Fibro-caseous disease with large cavities in both upper zones

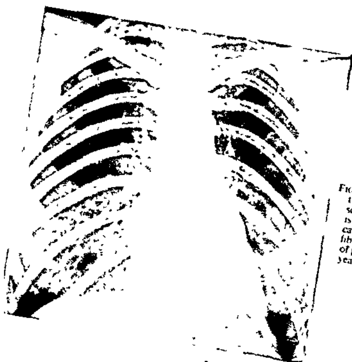


FIG 138 — Fibro-caseous tuberculosis, left second interspace This is considered fibro-caseous rather than fibroid on the history of progressive disease 3 years previously

latent. This change is responsible in many cases for the so-called "pendulum" process of the disease. An apparently quiescent lesion begins to give rise to symptoms and the x-ray shadow becomes a little less clear cut and larger. Very often the appearances are only slightly changed, and they give rise to much controversy in deciding whether the change is real or *is due only to a minor* difference in technique. A few weeks' rest settles things down, but recurrence tends to occur. When the condition is recognized collapse therapy should be undertaken, for permanent arrest will seldom be achieved without it.

Fibroid tuberculosis

If the condition is truly fibrous it implies that the tuberculosis is healed, but in the process of healing the tuberculosis may produce so much fibrous tissue, with associated areas of collapse, that great disability may occur. On the other hand there may be only a few puckered scars which are of no clinical significance. [illegible]

[illegible] drainage, but in the lower and middle lobes it may give rise to much ill health (*Figs* 139 and 140)

TUBERCULOUS TRACHEO-BRONCHITIS

Early in the nineteen-thirties it began to be realized that tuberculosis of the bronchi was a relatively common condition, and further experience has shown that it plays an important part in the development of the disease. The work of Coryllos (1933) and of Eloesser (1934) was of outstanding importance. It is rather strange that more stress was not laid on its presence by the morbid anatomists after Koch's discovery of the tubercle bacillus. Many observers, whose experience extends back to the period following World War I and to the time when radiology of tuberculosis of the lungs first came into its own, have been struck by the apparent increase in cases showing both clinical indication of the condition and radiological evidence of its presence, as shown by collapse and tension cavities. It is possible that this is another example of the change in the type of disease.

The method by which tracheo-bronchitis is produced is not yet decided. Certainly it is commoner in cases in which cavities exist *in connexion with the* affected bronchus, but there are many cases in which no cavity is present. It is *possible to demonstrate that many submucosal lesions* exist, probably in connexion with lymphatic channels. These need not be continuous, often there are interruptions in which the lymphatic vessels and submucosal areas are normal betwee[illegible] these tuberculous lesions [illegible] common factor [illegible] ther hand its predilection for areas where sputum stagnation *is common, and* [illegible] the neighbourhood of cavities, makes it likely that endobronchial implantation is also an important factor

Because definite diagnosis in life depends on bronchoscopy, *the importance* of the presence of lesions in the bronchi within bronchoscopic vision has been

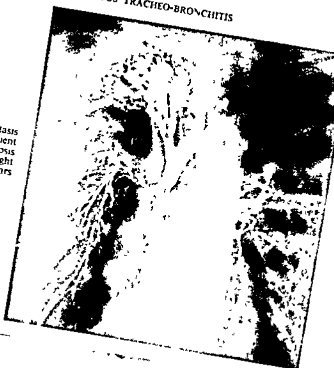


FIG 139—Bronchiectasis right upper lobe Patient had had tuberculosis with cavitation in right upper lobe many years previously

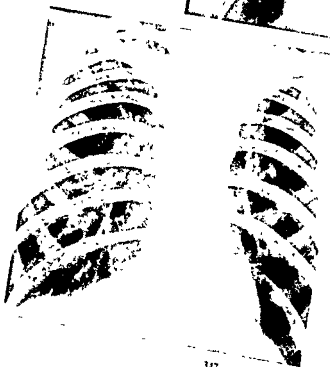


FIG 140—Collapsed left upper lobe fibrotic and calcified disease right apex

stressed, whereas actually its more common *presence in the smaller bronchi* plays a very important though less obtrusive part.

If the obstruction is in a lobar or main bronchus a large area of lung will be affected, hence tracheo-bronchitis causing obstruction is always of great immediate importance if within bronchoscopic vision, whereas if the lesion is *in the periphery* of the lung it may only produce the effects of the non-obstructive variety, owing to the small area of lung which is affected.

Non-obstructive tracheo-bronchitis

There are hardly any symptoms connected with this unless it occurs in a large or main bronchus If it is in the latter a troublesome irritating cough may be present, frequently with a considerable amount of sputum; this may interfere with the patient's rest. The cough may be of the "incomplete" type, although this is more apt to occur when obstruction is present The patient has bouts of coughing of a spasmodic type, which are very exhausting; before the sputum is brought up, exhaustion and shortness of breath lead to the cessation of the cough, following the cough there is a high negative pressure in the bronchi, and so the sputum which the cough has dislodged into the larger bronchi is sucked back into new areas, and spread is likely. Often the condition produces tubercle bacilli in the sputum, and this may lead to difficulty. Occasionally a persistent or intermittent positive sputum is found in the apparent absence of an adequate cause in the lung parenchyma, even after exhaustive radiological examination This is strongly suggestive of tracheo-bronchitis as a cause In fact, a presumptive diagnosis can be made on this finding alone, although other causes may be the pre-obstructive stage of the extrusion of a bronchial gland into the bronchus, or a tuberculous larynx.

This statement, of course, does not imply that the condition is primary. There is always a lung lesion, but it may be so small that it is undetected or easily missed.

If visible bronchoscopically, the tracheo-bronchial lesion varies from a slight localized reddening of the mucosa to an actual ulcer, with localized swelling and congestion as intermediate stages It is the small localized reddened areas which have led to the diversity of the reports on the frequency of the occurrence of tuberculous tracheo-bronchitis; some observers make a positive diagnosis on all of these, whereas others demand at least some swelling before considering the diagnosis to be definite. Non-obstructive tracheo-bronchitis may give rise to a slightly irregular temperature, but the erythrocyte sedimentation rate often remains completely normal This is a useful diagnostic pointer.

Obstructive tracheo-bronchitis

Three important effects may be produced by this form of disease: (1) interference with the aeration of the area distal to it; (2) interference with bronchial drainage, (3) an effect on the mobility of the bronchial walls.

Interference with aeration

On the basis of the fact that the bronchus elongates and widens on inspiration and that the reverse takes place on expiration, it is thought that obstructive emphysema is the normal result of obstruction, but this supposition fails to take into sufficient account two points: (1) the clogging effects of the presence of

bronchial secretions and the inflammatory condition in the distal part of th lung, (2) the considerable anastomosis which occurs between the pulmonar and the systemic circulation, by which air can be absorbed

Hence, in practice, obstructive emphysema in adults is by no means common. An analogous condition—inflation of cavities—is common; in fact, rapid alteration in the size of cavities is strongly suggestive of tracheo-bronchitis Around the cavities there is always an area where the elasticity of the lung is reduced by inflammation, and it is in the relatively small bronchi leading to the cavities that the secretions will be most abundant and produce a maximal effect A corollary of this lies in the occasional closure of cavities by alleged "kinking" of the bronchi, especially in the course of artificial pneumothorax treatment There is no real evidence that such kinking does take place, and it is far more likely that the effect is produced by swelling of the walls of the draining bronchi and by viscid secretions This viscosity is well recognized in bronchial obstruction due to a neoplasm Clegg (unpublished communication) has found out that in the bronchi leading to active cavities tuberculous inflammation is usual

Similarly, x-ray findings have been used to suggest that bronchial occlusion causes atelectasis In the active stages of tuberculosis, partial bronchial occlusion is common (though the part played by fibrous strictures, caused by an attempt to heal the bronchus, must be emphasized), but complete occlusion is certainly rare A prominent exception to this is the case of inspissated cavities The error is due to the limitations of bronchoscopy, to be certain, especially when inspecting the upper-lobe bronchi, that the occlusion is complete, is to ask too much of the method, but many reports indicate that this conclusion is drawn

Pure atelectasis in parenchymal tuberculosis, if it exists at all, is uncommon Apart from post-mortem findings, atelectasis uncomplicated by pneumonic and fibrotic processes is a completely reversible phenomena, but the number of cases with cavities treated by artificial pneumothorax, and showing atelectasis, in which complete re-expansion takes place, is certainly small (Figs 141–144)

Accordingly, the following results may occur as a result of interference with aeration

(1) Obstructive emphysema (rare)

(2) Ballooning and frequent alteration in the size of the cavities (This effect is proved if the intracavity pressure is found to be above the atmospheric level)

(3) Comparatively rapid diminution of the size of a lobe or segment (The rarity of pure atelectasis is shown by the fact that these areas commonly do not shrink, at any rate immediately, to the size of a purely atelectatic lobe)

(4) Rapid diminution in size of one lobe, as compared with the others, under pneumothorax treatment

(5) Pendulum movement of the mediastinum, showing marked difference of intrapleural pressures

(6) Production of dyspnoea and pain

There is nothing in the presence of tracheo-bronchitis or in the amount of lung put out of action, which will account for these symptoms The pain is a dull ache in character and only roughly localized to the area affected Both symptoms are most apparent when marked changes of lung volume occur suddenly, producing

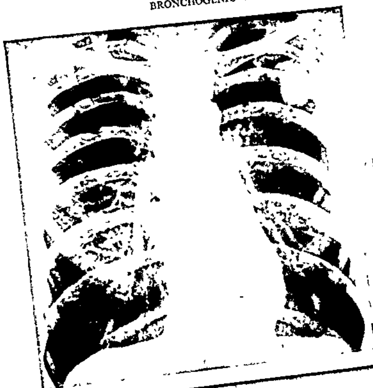


FIG 141— Inspissated cavity following re-expansion of artificial pneumothorax

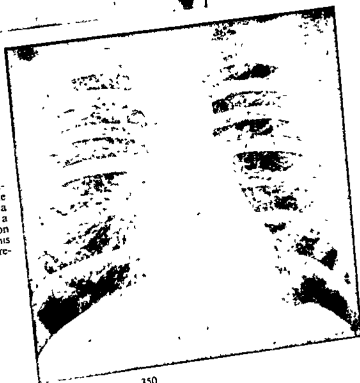


FIG 142 —Subclavicular rounded discrete shadow This is a blocked cavity, a definite cavity lesion being present in this situation 1 year previously

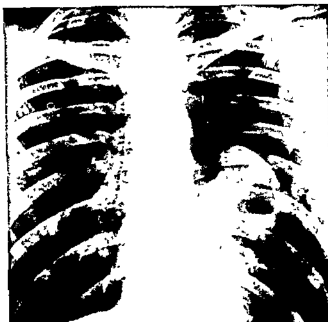


Fig. 143 —Collapsed upper lobe with cavity under pneumothorax At bronchoscopy the bronchus was nearly occluded, and 5 years later the lobe had shrunk behind the heart and the cavity had closed

a high negative pressure as a result of bronchial blockage, they disappear when aeration re-occurs, or more gradually if lung shrinkage becomes permanent.

(7) The presence of a "wheeze". This is the most characteristic symptom of tuberculous tracheo-bronchitis It is, of course, not confined to these cases, but a localized wheeze, felt and heard by the patient and by the observer in a case of pulmonary tuberculosis, is practically diagnostic. It is often most obvious to the patient when he is lying down and in a particular position It may cease when a blob of sputum is coughed up, but it soon reappears Frequently, of course, the condition is diagnosed as asthma but its localization should obviate this

Interference with bronchial drainage

Such interference produces the following results

(1) Marked and repeated changes both in the quantity and the quality of the sputum.

(2) The appearance of fluid levels in the cavities, and complete filling of cavities leading to inspissation of them

(3) Sudden disappearance and reappearance of large numbers of tubercle bacilli in the sputum

(4) Toxic phenomena associated with sputum retention Considerable evidence

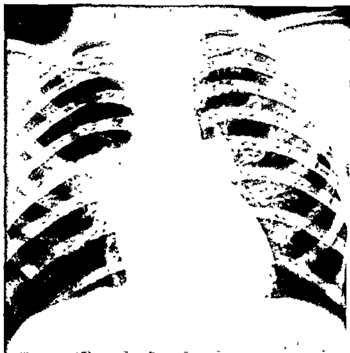
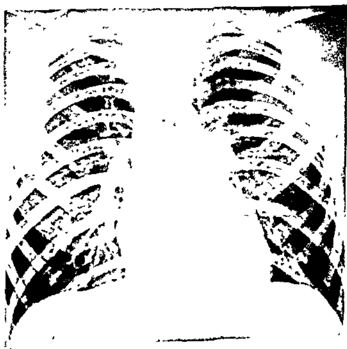


FIG 144 —Epituberculosis There is collapse of the pectoral segment of the upper lobe with an inflammatory reaction around it. This had practically disappeared 10 weeks later.

(a)



(b)

cultivation Certainly foetor of the breath frequently occurs when the contents of cavities which have been blocked are coughed up

The toxic phenomena comprise sudden brief spikes of temperature often without corresponding rise in the erythrocyte sedimentation rate, rigors, and loss of appetite, there is often a polymorphonuclear leucocytosis.

Interference with the mobility of the bronchial walls

The effects of this are, of course, most obvious when cicatrization has occurred, but it is probable that, even in the earlier stages, the "lifting" of sputum in the affected areas is interfered with This retention of sputum will play a considerable part in the bronchial blockage, and its effect is exaggerated when, under a pneumothorax, the bronchial action of elongation and widening in inspiration is reduced It is the probable explanation of the "absorption" lobar collapse, which frequently occurs in pneumothorax treatment This often persists when expansion of the lung is desired and is serious when the middle and lower lobes are affected A permanently collapsed upper lobe is of less importance The risk of the unexpandable lobe, the ballooning of unsupported cavities and pleural complications, make artificial pneumothorax a hazardous method of treatment in these cases

Prognosis

The account given above of the possible results of tuberculous tracheo-bronchitis will have indicated that it is likely to have a deleterious effect on the evolution of the tuberculous process in the individual case, particularly by increasing toxaemia, promoting bronchogenic dissemination and interfering with cavity healing Even when healing takes place, some stenosis is often produced and the changes produced in the bronchial wall make bronchiectasis a common sequence On the other hand, occasionally it plays a part in cavity closure, by occluding the bronchus and allowing the air in a cavity to be absorbed, with resultant closure In favourable circumstances there may be little or no sputum retention and a soundly healed scar may be produced, in other cases in which drainage has been interfered with, an inspissated cavity may be left

Whatever the exact methods of action, examination of resected material shows that tracheo-bronchitis is a major factor in the prevention of cavity closure In a series of 80 cases collected by myself, macroscopic tracheo-bronchitis or stenosis in the bronchi leading to the cavities was found in 75 per cent of the cases in which resection was performed for the treatment of persistent cavities

BIBLIOGRAPHY

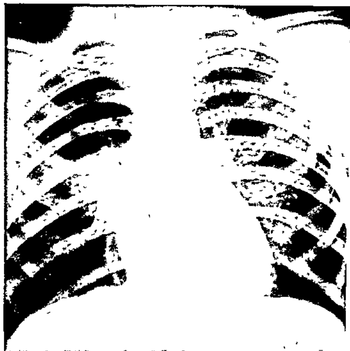
Abeles, H, and Pinner, M (1941) "Accidentally Discovered Pulmonary Tuberculosis" *Amer Rev Tuberc*, 49, 490

Amberson, J B, Jun (1942) "Features of the Early Pulmonary Infiltration" *Amer Rev Tuberc* 45, 660

Assman, H (1927) "Ueber die instraklavikulaeren Lungerum Filtrationem im Beginn der Tuberculose Jugendlicher Erwachsener und ihr Schicksal" *Dtsch mead. Wschr* 53, 781

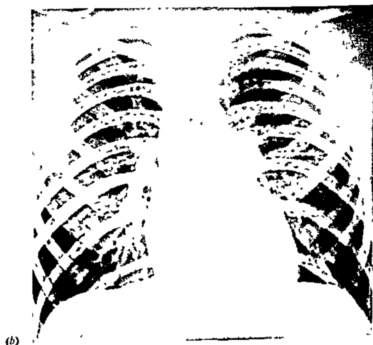
Bobrowitz I D, and Dworke, R E (1946) The Early Diagnosis of Minimal Pulmonary Tuberculosis" *New Engl J Med*, 234, 10

Braeuning, H (1938) *Der Beginn der Lungentuberkulose beim Erwachsenen* Leipzig



(a)

FIG 144—Epituberculosis There is collapse of the pectoral segment of the upper lobe with an inflammatory reaction around it. This had practically disappeared 10 weeks later.



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BIBLIOGRAPHY

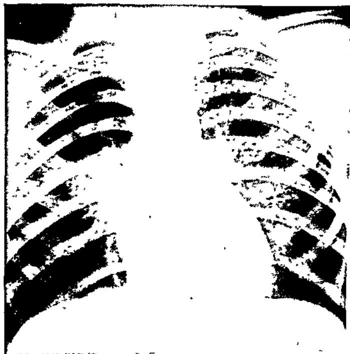
Abeles, H, and Pinner, M (1941) "Accidentally Discovered Pulmonary Tuberculosis" *Amer Rev Tuberc*, 49, 490

Amberson, J B, Jun (1942) "Features of the Early Pulmonary Infiltration." *Amer Rev Tuberc*, 45, 660

Assman, H (1927) "Ueber die insraklavikulaeren Lungenin Filtrationem im Beginn der Tuberculose Jugendlicher Erwachsener und ihr Schicksal." *Dtsch med W schr*, 53, 781

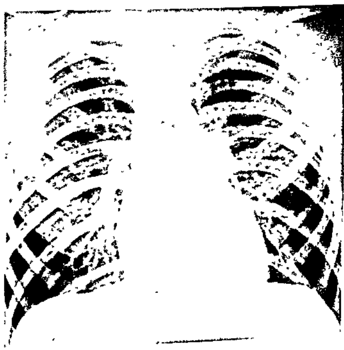
Bobrowitz, I D, and Dworke, R E (1946) "The Early Diagnosis of Minimal Pulmonary Tuberculosis" *New Engl J Med*, 234, 10

Braeuning, H (1938) *Der Beginn der Lungentuberkulose beim Erwachsenen* Leipzig.



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BIBLIOGRAPHY

Abeles, H , and Pinner, M (1941) "Accidentally Discovered Pulmonary Tuberculosis" *Amer Rev Tuberc*, 49, 490
Amberson, J B , Jun (1942) "Features of the Early Pulmonary Infiltration" *Amer Rev Tuberc*, 45, 660
Assman, H (1927) "Ueber die insraklairkulaeren Lungerim Filtrationem im Beginn der Tuberculose Jugendlicher Erwachsener und ihr Schicksal" *Dtsch mead Wschr*, 53, 781
Bobrowitz, I D , and Dworke, R E (1946) "The Early Diagnosis of Minimal Pulmonary Tuberculosis" *New Engl J Med*, 234, 10
Braeuning, H (1938) *Der Beginn der Lungentuberkulose beim Erwachsenen* Leipzig

Brooks, W. D. W (1944) "Management of Minimal Pulmonary Tuberculosis—disclosed after fluorography." *Lancet*, **1**, 745.

Chang, R. (1948) "Minimal Pulmonary Tuberculosis Prognostic Significance of Positive Sputum after Adequate Treatment for T B" [illegible]

Christie, R V (1934) [illegible] Significance" *J.* [illegible]

Coryllos, P N. (1933) [illegible] *Rev Tuberc.*, **28**, 1

Eloesser, L. (1934) "Bronchial Stenosis in Pulmonary Tuberculosis" *Amer. Rev Tuberc*, **30**, 123

Israel, H L, and Longer, E R. (1941) "Primary Tuberculosis in Adolescents and Young Adults" *Amer Rev. Tuberc*, **43**, 42

Jaches, L, and Wessler, H (1923) *Clinical Roentgenology of the Chest*

Kayne, G G, Pagel, W, and O'Shaughnessy, L (1948a) "Aspiration Type of Congenital Tubercle" and further communication in *Pulmonary Tuberculosis*, p 12 Oxford; Oxford University Press.

— — — (1948b). *Ibid*, p 206.

Lange, B (1934) "Beitrage zu Lungenkrankheiter" *Dtsch. Med Wschr*, **60**, 197.

Lloyd, W. E, and MacPherson, A M (1933) "A Reinvestigation of Children Previously Examined by Tuberculin Tests" *Brit med J.*, **1**, 818.

Madsen, W., Holm, J, and Jansen, K A (1942) "Studies in the Epidemiology of Tuberculosis in Denmark" *Acta Tuberc Scand*, Suppl No 6

Malmros, H., and Hedvall, E (1940) "Primary Tuberculous Infection in Adults." *Amer. Rev Tuberc.*, **41**, 563

Medlar, E M (1948) "The Pathogenesis of Minimal Pulmonary Tuberculosis" *Amer. Rev Tuberc*, **58**, 583

Nayer, H R, and Pinnes, M (1942) "Chronic Pulmonary Tuberculosis" *Amer. Rev. Tuberc.*, **46**, 505

Pagel, W (1935) "On the Endogenous Origin of Early Pulmonary Tuberculosis. The Anatomic View of its Clinical Diagnosis" *Amer J. med Sci*, **189**, 253

Pinner, M (1945). *Pulmonary Tuberculosis in the Adult*, p 171. Springfield, Ill, Thomas.

Plunkett, R E, and Mikor, E X (1940) "Unrecognised Tuberculosis in General Hospitals" *Amer Rev Tuberc*, **41**, 381

Pottegen, F M. (1949) "Toxicity of Sputum Digestants to Tubercle Bacilli in Water and Sputum" *Amer Rev. Tuberc*, **60**, 629

Prophit Tuberculosis Survey (1948a) *Tuberculosis in Young Adults*, p 51 London; Lewis.

— (1948b) *Ibid*, p 104

— (1948c) *Ibid*, p 105

— (1948d) *Ibid*, p 164

Reisner, D (1948) "Insipiency and Evolution of Pulmonary Tuberculosis." *Amer. Rev. Tuberc*, **60**, 629

Rich, A R (1944a) *Pathogenesis of Tuberculosis*, p 655. Springfield, Ill; Thomas

— (1944b) *Ibid*, p. 881

Smith, C R. (1949) *Amer Rev. Tuberc*, **57**, 207

Wingfield, R. C (1936) "Latest Adolescent Pulmonary Tuberculosis" *Brompton Hosp. Rep*, **5**, 10

Wittkower, E D (1949) *A Psychiatrist Looks at Tuberculosis* London; National Association for the Prevention of Tuberculosis

Young, F. H, and Ganz, E (1941) "The Persistence of Lipiodol in the Lungs following Bronchography." *Brompton Hosp Rep*, **6**, 107

CHAPTER 14

PLEURAL TUBERCULOSIS

F. H. Young

AETIOLOGY

In view of the anatomical relationship between the lungs and the pleura, it would be surprising if pleural involvement were not common in pulmonary tuberculosis The confirmation of this probability is found in the relative frequency with which pleural adhesions are found when an artificial pneumothorax is attempted. Even when adhesions are not found between the parietal and visceral pleurae, it is common to find interlobar symphysis

Secondary tuberculous pleurisy

For practical purposes it may be assumed that tuberculous pleurisy, especially with effusion, is secondary to sub-pleural pulmonary tuberculosis or to tuberculosis of adjacent structures This does not imply that there must be an actual communication between a sub-pleural tuberculous focus and the pleural cavity, for the sub-pleural lymphatic vessels drain distally towards the pleura Experimentally, tubercle bacilli introduced into the pleura of experimental animals can produce a pleural effusion, if the animal has had no experience of tuberculosis the number must be large, but if it is sensitized the number required is relatively small

Because the hypersensitivity of the naturally infected human being is often much higher than can be produced in the experimental animal, it is easy to see how a large outpouring of fluid may follow the introduction of a small number of bacilli into the pleural cavity, whether from the lung or elsewhere Rich (1944) states that he is unable to find in the literature any instance in which intravascular injection of tubercle bacilli has produced a pleural effusion directly, but sparse miliary pleural tubercles are common, and it may be that the greater hypersensitivity in the human subject may alter this If so, a haematogenous seeding of tubercle bacilli into the pleura may be expected to produce an effusion, should the degree of hypersensitivity be sufficiently large The question must remain difficult to answer on a basis of proof, one way or the other

There is some evidence that collateral effusions occur, of a nature similar to the serous effusions which are seen associated with pneumonia treated with sulphonamides It is possible that these are effusions of a type which clears up unexpectedly rapidly Apart from this, it seems reasonable to suppose that all pleurisy of tuberculous origin is due to sub-pleural or juxta-pleural tuberculous foci If there is a discharge of tuberculous material into the pleura an effusion will probably occur, its extent will depend on the result of the product of the number of bacilli discharged and the degree of hypersensitivity of the individual.

Stage of pleural involvement

Pleural involvement seems to occur in all stages of tuberculosis. It is common

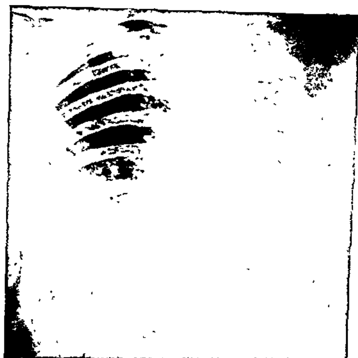


FIG 145 —*Simultaneous bilateral tuberculous effusion*

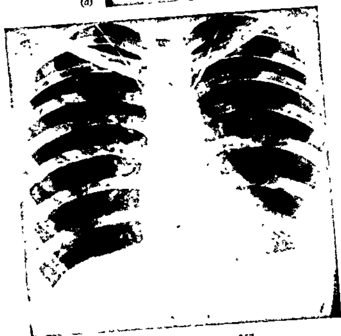
to find evidence of pleural thickening in association with primary foci How often pleural effusions occur as the direct result of the primary focus is uncertain They occur in children, especially in the interlobar spaces, but if an effusion followed frequently as a direct result of the primary focus, one would have expected such effusions to occur more frequently The commonest age-group for occurrence of pleural effusion is in adolescents, but in these the period which elapses between the primary infection and the effusion is usually a matter of months rather than weeks ; hence an early post-primary dissemination seems to be a more probable cause. In such effusions it is common to find scattered tubercles on the pleura ; when the effusion is simultaneously or successively bilateral, it is almost certain that early post-primary dissemination is the cause, for the occurrence of extra-pulmonary foci connected with bilateral pleural effusion is very common (Figs. 145 and 146). *All pleural effusions are not due to such early dissemination* In many cases there is evidence of pre-existing pleural adhesions and of bronchogenic pulmonary tuberculosis with or without cavitation. In these the effusion may be due either to a direct spread from the bronchogenic focus or to a late dissemination unconnected with the primary lung focus Because in this type extrapulmonary foci are relatively uncommon, a direct spread from a bronchogenic pulmonary lesion is the more probable cause

Relation to post-primary and bronchogenic lesions

The proportion of pleural effusions associated with early post-primary dissemination and bronchogenic tuberculosis is roughly indicated in the Prophit Tuberculosis

Fig 146 —Consecutive bilateral pleural effusion, (a) 10 11 44, (b) 9 11 45 At the time of the first effusion there was already infiltration at the left apex

(a)



(b)

Survey (1948) of young adults Among cases of minimal tuberculosis, occurring in individuals who had been previously Mantoux negative, pleural effusions occurred in one-third of the number (Fig 147); among similar cases in which the Mantoux test had been positive, in only about 12 per cent did effusions develop which were thus associated with bronchogenic tuberculosis Even this figure is probably too high, for a majority of the patients only reacted to a large test dose of tuberculin; this suggests the possibility of error, or that reversion of the test might have been in progress. In the early post-primary effusions the proportion of "primitive community" cases was very high (For definition of a primitive community, see page 343.) This was not so in the other groups

Whenever the sub-pleural focus pursues an indolent course and the hypersensitivity is comparatively low, the pleural surfaces become adherent and so no effusion can take place (Fig 148) Consideration of the common situation of adhesions, as revealed by the induction of artificial pneumothorax, shows that the
the upper lobe, (3) over
posterior surface of the
In the last-mentioned
site the adherence is commonly over a much wider area than in the other sites The first four are areas where bronchogenic tuberculosis is common, but in the early stages it is not very common at the base Presumably here the effusion is caused by tuberculous material, shed by one of these sites, which gravitates downwards and produces a diffuse inflammatory reaction, thus causing widespread adherence at the base, whereas in the other areas adherence takes place over the local area of breakdown only. If this theory is accepted, small effusions must be of much commoner occurrence than clinical findings would lead one to suppose.

Extension from extrapulmonary abscesses

A pleural effusion may also be due to contact infection of the pleural cavities from a tuberculous abscess of the spine or caseous glands adjacent to it Sometimes a bilateral effusion may result.

Effects of pulmonary collapse

An interesting speculation relates to the part played by collapse of a lung segment. Undoubtedly, in the presence of artificial pneumothorax, the onset of fluid follows a local collapse in an undue number of cases; it may be a factor in other cases of pleural effusion in which unduly long persistence of fluid occurs without marked pleural thickening Presumably lack of expansion of part of the lung must be a factor in causation At the same time, by analogy with the artificial pneumothorax cases, it seems highly probable that there is a
material
thus and

Idiopathic pleurisy

The extent to which tuberculosis is responsible for cases of pleurisy, with or without effusion, for which no other definite cause can be discovered has been the subject of much discussion Scadding, Nicholson and Hoyle (1951) have noted that, in almost all the cases in which a history of pain

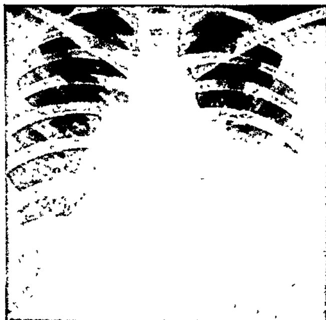


FIG 147.—Illustrating occurrence of pleural effusion after early infiltration Film, January 1948, no abnormality, film, August 1948, early infiltrate left subclavicular region, 11 1 49, pleural effusion This girl had been sent home to rest following the appearance of the lesion, and was wrongly advised to take plenty of exercise in the open air



FIG 148.—Spontaneous pneumothorax with fluid, presumably from perforation adjacent to apical adhesion

suggesting pleurisy could be obtained, adhesions were present when an artificial pneumothorax was induced On the other hand, it is comparatively uncommon to be able to obtain a history of pleural pain or of definite pleurisy from patients in whom a pleural effusion subsequently develops. I have not been able to trace any series of cases in which patients suffering from "dry pleurisy" have been submitted to Mantoux tests It seems probable, however, that any definite case of idiopathic pleurisy should be treated as tuberculosis suspect, until a negative tuberculin test has disproved it

Discovery of tuberculous infection

In cases with effusion we are on much safer ground. The percentage of cases of pleural effusion of undetermined origin varies inversely with the care which is taken to recover tubercle bacilli Series have been reported in which tubercle bacilli have been demonstrated in up to 70 per cent of cases, and in cases in which there was other evidence of tuberculosis up to 90 per cent produced evidence of tubercle bacilli when the most stringent methods of examination were employed In young people the presumption of tuberculosis is so great that, unless a careful review of the case suggests some other definite cause, tuberculosis should be diagnosed and receive adequate treatment

In middle-aged or old patients, pleural effusions are usually associated with the bronchogenic type of disease In these there is usually some radiological or other evidence of tuberculosis of adjacent organs This, of course, may not be forthcoming until the absorption of the fluid allows adequate radiological examination Especially in men, large persistent effusions are more often due to neoplasms The possibility that tuberculosis of the spine is present must not be overlooked.

CLINICAL FEATURES OF TUBERCULOUS PLEURAL EFFUSION

It is unnecessary here to recapitulate the physical findings.

The onset, as stated above, is often closely associated with the results of the primary complex Malmros and Hedvall (1940) reported 6 cases of pleural effusion out of 47 tuberculous cases in which a negative Mantoux reaction had been obtained some time previously and similar reports have been published in the Prophit Tuberculosis Survey (1948) In children an association with erythema nodosum has been noted

Any evidence combating the idea that effusions occur commonly in later post-primary dissemination is invalidated by the frequent occurrence of small symptomless effusions Chance radiographs give abundant evidence of their existence, but whether or not pleural involvement, demonstrated in the costo-phrenic angle, can be taken as definite evidence of previous pleural effusion must await further research

The authors of the Prophit Survey stated that, when pleural effusion developed in cases which were Mantoux positive at the beginning of the Survey, their appearance was always accompanied by high fever ; presumably this was so also in the cases in which the Mantoux reaction was negative on entry, although the authors do not say so However, Myers (1935) reports that in 30 cases of tuberculous pleural effusion, in which there was no evidence of parenchymal disease, 10 cases

had a subacute onset and in 12 the onset was insidious; only 8 cases had the classical acute onset. Myers does not state the age of the patients.

There is some possibility that pleural effusions associated with bronchogenic or late post-primary tuberculosis have a less serious prognosis, as regards development of progressive pulmonary tuberculosis, than have the early post-primary types. The Prophit authors state that, in their series of 12 cases, in none had pulmonary tuberculosis developed at the end of 2½ years' observation. It is generally accepted that this is the period during which pulmonary tuberculosis is likely to follow a pleural effusion, though an appreciable number do occur in later years, so these 12 cases had passed the most dangerous period. Most authors have found that in a certain proportion of cases (varying from 20 to 30 per cent) of pleural effusion, bronchogenic or other forms of tuberculosis develop.

It has been alleged that the height and persistence of the fever and the size of the effusion are factors which can be used to determine its prognosis. If this were proved it might be of great value in determining the amount of treatment which should be given in each case. Slow clearing of the effusion suggests that a communication may exist between the pleurae and the lung, and persistence of the fever may indicate in some cases that fever-producing foci accompany the effusion. If this is so, the prognosis is obviously less favourable, but the degree of hypersensitivity is certainly a considerable factor and the effect of this is undecided.

TREATMENT OF PLEURAL EFFUSION

The treatment of tuberculous pleural effusion is still a matter on which opinions differ. The points which must be taken into account are (1) the likelihood of subsequent development of pulmonary tuberculosis and (2) the possibility of failure to achieve full re-expansion either because of bronchial blockage or of pleural thickening.

Cases due to early post-primary dissemination

If the effusion is the result of an early post-primary dissemination, no local treatment is likely to affect the subsequent development of pulmonary tuberculosis. The individual's general resistance must be supported by rest and hygienic measures. Rest in bed should be the rule until all evidence of fluid has disappeared and the temperature and erythrocyte sedimentation rate have become normal. At this stage the disseminated bacilli should be open to attack by antibiotics, and it would seem logical to give, at least to all members of primitive communities, a course of streptomycin and *para*-aminosalicylic acid for 6 weeks; this is unlikely to give rise to resistant organisms. No series of cases in which uch treatment has been tried has yet been published.

ases of supposedly bronchogenic origin

When the effusion is thought to be associated with bronchogenic disease, e are presumably dealing also with a localized intrapulmonary lesion. It is these cases that the use of temporary phrenic interruption, preferably with a eumoperitoneum for the first few months, would seem to be a reasonable ethod of treatment. If this is started as soon as the effusion has commenced disappear, a good relaxation of the lung can be obtained. This relaxation

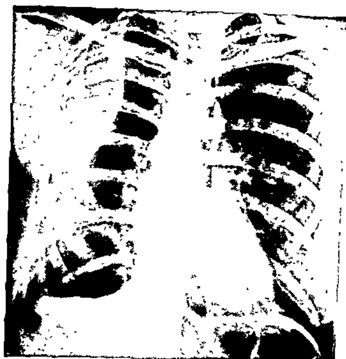


FIG 149 — Encysted pleural effusion unchanged during the previous three years.

(it may be hoped) will promote healing of the sub-pleural focus and help to close any lung perforation which is keeping up the effusion. Maurer (1946) has published a series of cases, and in my own hands the result seems to be beneficial in the small series of cases in which it has been tried

Cases complicated by a bronchial block or pleural thickening

Failure to achieve re-expansion is due either to bronchial block or pleural thickening In an effusion the former must generally be caused by tracheo-bronchial tuberculosis or by external pressure on the bronchi by tuberculous glands In either of these conditions the use of streptomycin and *p*-amino-salicylic acid would seem to be indicated

Gross thickening of the pleura, with subsequent failure of the lung to expand fully, is not very common, owing to the fact that a pleural effusion (apart from an artificial-pneumothorax effusion) seldom becomes purulent; but if such thickening occurs it is of serious import, sometimes a persistent serous effusion will produce pleural thickening (Fig 149). In the past, opinions have differed on the question of aspiration of the fluid, with or without air-replacement. The present consensus of opinion is against aspiration, except as a diagnostic measure or when the bulk of the fluid produces distress—actually this is produced rather by the rate of formation than by the actual amount of fluid Air-replacement with continuation of the pneumothorax is now seldom performed owing to frequent production of tuberculous empyema Here, again, the use of streptomycin

seems worthy of consideration when pleural thickening seems likely The use of 1 gramme of streptomycin intrapleurally every 2 days with similar aspiration of small amounts of fluid simultaneously, is certainly of value in some cases of fluid following adhesion section in artificial pneumothorax The lung can be seen to expand on inspiration, with a displacement of the fluid upwards in a way quite unusual when only an expectant treatment has been carried out

Simultaneous administration of tuberculin and streptomycin

The discovery by Honor Smith, of the Meningitis Unit at Oxford, that, by the use of tuberculin simultaneously with streptomycin, the deposition of gelatinous material at the base of the brain can be largely avoided (Smith, 1950), has led to the discovery at Brompton that, in bronchogenic and pulmonary tuberculosis, the use of this combination allows the individual to tolerate relatively enormous doses of tuberculin with little general or focal reaction and with the loss of skin sensitivity to the intradermal injection of pure tuberculin If, as is assumed, hypersensitivity is an important fact in the production of pleural effusions, its abolition even temporarily would seem indicated It would seem that the combination is worth an extended trial in pleural effusion cases

TUBERCULOUS EMPYEMA

Tuberculous empyemas occur in the vast majority of cases as the result of the opening of a caseous focus in the lungs or pleura into the pleural cavity In cases where the resistance of the patient is low a serous pleural effusion may become purulent without any interference, but this is not common Usually it occurs as the result of repeated aspiration, especially if the effusion is replaced with air.

The majority of cases arise as the result of a hydropneumothorax (Fig 147) This may occur spontaneously following a spontaneous pneumothorax When the cause of the pneumothorax is tuberculous, fluid quickly appears and soon becomes purulent , a valvular perforation is common and a mixed infection often results The patient is very ill, and a positive pressure is usually found with dyspnoea and cyanosis owing to the displacement of the mediastinum and interference with the contralateral lung

The other common cause is as a complication of artificial pneumothorax It has been said, and it is certainly true that the efficiency of a pneumothorax clinic may be measured by the percentage of tuberculous empyemas which occur in it There are two main causes (1) the persistence of this form of treatment when dangerous adhesions are present, every artificial pneumothorax should be a "trial" pneumothorax , and (2) injudicious adhesion section Hence the main form of treatment is such skilful conduct of pneumothorax treatment that tuberculous empyemas do not occur When the work is good mixed infection empyemas are also rare , the usual cause is failure of aseptic technique, and the continuance of a pneumothorax when underlying cavities persist , in the latter it is especially dangerous to continue the treatment when an adhesion is adjacent to the cavity bearing area , the adhesion ruptures and an empyema results

The diagnosis of tuberculous empyemas depends on the recognition that fluid is present and regular diagnostic aspiration with a fine needle. When air is not already

present care should be taken to avoid allowing it to enter the pleural cavity, as effusions are more likely to become purulent if air is present.

Treatment of tuberculous empyema

The prime object of treatment is the obliteration of the pleural space by re-expansion of the collapsed lung The pleural cavity should be aspirated at least twice a week, and 1 gramme of streptomycin, and 20 millilitres of a 20 per cent solution of P A S put in on the occasion of each aspiration. The patient should lie with the site of the puncture uppermost for two hours to help to avoid the production of a sinus, and the back should be avoided if possible, in case a thoracoplasty is necessary subsequently The treatment should be continued until all hope of re-expansion has been abandoned If re-expansion is unsuccessful or the pleura is already thick a thoracoplasty will be necessary to obliterate the space When the resistance is good, and no other contra-indication is present a pleurectomy with resection of the underlying tuberculous tissue has been advocated So far the results are promising, but it is essential that the tubercle *bacilli are streptomycin sensitive It is indicated especially when the disease is in* the lower half of the lung or when there is an obvious broncho-pleural fistula. Drainage should be avoided for a pure tuberculous empyema

Occasionally a small encysted tuberculous empyema might be allowed to remain (Fig 148) It may only be advocated in patients with a high resistance, and in whom a residual cavity in the lung is excluded, and when all evidence points to arrest of the disease in the lung

Treatment of tuberculous (mixed infection) empyema

The nature of the secondary infection should be determined, and the sensitivity to the various antibiotics determined If sensitive, the appropriate antibiotic should be used intrapleurally and by intramuscular injection in an endeavour to eradicate the secondary infection If successful the case can then be treated as a pure tuberculous empyema, but if there is a broncho-pleural fistula this is unlikely A closed intercostal drain can then be tried, but open drainage will often be necessary As soon as the general condition of the patient permits he should be submitted to thoracoplasty Frequently a sinus will be present, and this will have to be dealt with later by a plastic operation or decortication if the underlying disease is arrested

BIBLIOGRAPHY

Malmros, H , and Hedvall, E (1940) "Primary Tuberculous Infection in Adults" *Amer. Rev. Tuberc*, 41, 563.
Maurer, G (1946) "Paralysic artificielle du diaphragme et pneumoperitonic" *Schweiz Z Tuberk* 3, 313
but d'eviter des suites elognées"
risy with Effusion" *Brompton*
Adults, p 168. London, Lewis.
ingfield, Ill., Thomas
Pneumothorax" *Quart J. Med*,
20, 313

CHAPTER 15

CLINICAL PATHOLOGY OF PULMONARY TUBERCULOSIS

J. W. CLEGG

THE CLINICAL pathologist has two distinct functions to perform in assisting the clinician with the problems of pulmonary tuberculosis. First, he is of assistance in the diagnosis of the condition for this remains incomplete until *Mycobacterium tuberculosis* has been demonstrated in the tissues or excretions of the patient. Secondly, he can give valuable help in assessing the results of treatment. This function has been greatly extended since the introduction of satisfactory chemotherapeutic agents against *Myco. tuberculosis* and the importance of avoiding drug resistance to these agents was demonstrated. Furthermore, the conversion of a patient's sputum from positive to negative for *Myco. tuberculosis* remains the most important single criterion of adequate and satisfactory treatment.

While the laboratory methods employed in both these functions are often identical, the interpretation of the results may differ with the function for which they are employed. For example, while the demonstration of scanty acid-fast bacilli in the sputum of a suspected case of pulmonary tuberculosis may not carry diagnostic conviction, the same observation in a known case of pulmonary tuberculosis which has previously undergone sputum conversion following successful pneumothorax treatment is of great significance. It is proposed, therefore, to give a brief account of the laboratory procedures which are employed, and then attempt an assessment of their value.

The laboratory methods may be divided for convenience into 6 groups:

(1) The microscopical examination of excretions or pathological exudates for the presence of acid-fast bacilli.
(2) Cultural methods for the growth of *Myco. tuberculosis*.
(3) Animal inoculation to demonstrate virulent *Myco. tuberculosis*.
(4) Sensitivity tests.
(5) Serology.
(6) Histological examination of biopsy material.

Microscopical examination of excretions or exudates

This is the most widely employed laboratory investigation in tuberculosis and has the great merit of speed. A report on the presence or absence of acid-fast bacilli in a given specimen is available in a few hours. Unfortunately, there is no method of differentiating between pathogenic *Myco. tuberculosis* and non-pathogenic acid-fast saprophytes under the microscope. This valid objection is probably rather over-emphasized and the method has a wide field of usefulness. Mycobacteria are, by definition, a group of bacteria which, when stained, resist decolorization with acid and alcohol. Since 1894 the Ziehl-Neelson technique has been the accepted standard procedure all over the world. In this method the bacilli on the film are stained with carbol-fuchsin, decolorized

with acid alcohol and the film counter-stained with methylene blue. The acid-fast bacilli thus appear under the microscope as red rods against a blue background. Owing to their small size, the bacilli must be searched for using a $\frac{1}{12}$-inch oil immersion objective To search over an entire film is thus a long and tedious job

It is a well recognized fact that a body
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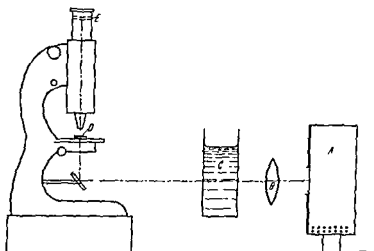


FIG. 150 —Diagram illustrating examination by fluorescent microscopy (*see* text for technique)

dyes (Lempert, 1944). Fluorescence is a property which many substances possess If these substances are stimulated by waves in the invisible near ultra-violet region, this stimulus excites them to emit waves of a higher wavelength in the visual spectrum When auramine, the dye most widely used in this technique, is stimulated by ultra-violet light it emits bright golden-yellow light. In the fluorescence method, therefore, a smear of the material to be examined is made in the usual manner. This is then stained with an auramine-phenol mixture and decolorized with an acid-alcohol mixture. It is then counter-stained with potassium permanganate Thus, as in the Ziehl-Neelson method, all mycobacteria will stain positively and neither stain is specific for *Myco tuberculosis*

violet light, passes through the sub-stage condenser of the microscope in the

is placed in the microscope tube to cut out all ultra-violet light which would be harmful to the eye With this technique auramine-stained bacilli are easily seen with a $\frac{2}{3}$ objective and any suspicious yellow specks may be quickly examined and the presence of acid fast bacilli is confirmed with the $\frac{1}{6}$ objective. If the bacilli appear in any way atypical the field can be marked on the slide and the smear then stained with the Ziehl-Neelson technique in the normal way In practice, this is seldom necessary. The fluorescence is at least as sensitive as the Ziehl-Neelson technique (Clegg and Foster Carter, 1946) and much more rapid With a $\frac{2}{3}$ objective the whole film may be examined in about 3 minutes whereas this takes at least 10 minutes with a $\frac{1}{12}$ objective In a laboratory handling large numbers of specimens it results in a marked saving in time and expense.

Cultural methods for the growth of *Myco. tuberculosis*

Myco. tuberculosis is a slow-growing organism. Even when seeded on a culture medium favourable to its growth an inoculum containing viable tubercle bacilli may take from 2 to 8 or more weeks to produce a recognizable colony The length of time taken depends upon the number of viable bacilli in the inoculum, the smaller the number the longer the time Obviously, if other bacteria are present in the material to be examined, these will overgrow the whole surface

viable tubercle bacilli from the whole specimen into a small volume, for the larger the number of bacilli used the quicker the growth will become evident Fortunately, mycobacteria are far more resistant to the action of acids and alkalis than other bacteria and the most satisfactory methods of concentration are based on this difference

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time interval between the lethal exposure of contaminating organisms and lethal exposure of mycobacteria to 4 per cent sodium hydroxide is short, being only about 20 minutes With modern centrifuges it is possible to spin 36 specimens at a time and if Petroff's method is employed all 36 specimens must be neutralized with 8 per cent hydrochloric acid within 20 minutes of stopping the centrifuge or false negative results will occur This time margin is too small for safety in a large routine laboratory, though Petroff's method probably remains the best for small numbers of specimens In the survey it was found that the tri-sodium-phosphate method (Corper and Stone, 1946) gave almost as good results as the Petroff technique and, as the action of tri-sodium-phosphate is much slower, there is little danger of killing the mycobacteria as well as the contaminating organisms On the other hand, the specimen must be incubated over-night with tri-sodium-phosphate and this introduces another delay of 1 day In both cases the neutralized centrifuged deposit is inoculated on to a minimum of 2 tubes of Lowenstein-Jensen medium and incubated at 37° C. All culture tubes are examined at weekly intervals and all bacterial colonies are examined under the

microscope. If acid-fast bacilli are present in a colony which has the morphological appearance of *Myco tuberculosis* the colony is subcultured on to agar and incubated at 37° C for 1 week. If the organism is a non-pathogenic saprophyte, growth will occur before the end of the week. If no growth occurs on the agar the organism is reported as *Myco. tuberculosis.*

Recently many methods have been described which attempt to speed up the technique of primary isolation of *Myco. tuberculosis.* One of the most successful is the slide culture technique of Pryce (1941). The material to be cultured is spread on a microscope slide and treated with acid to kill off contaminating bacteria. After neutralization the whole microscope slide is immersed in a laked blood medium and incubated at 37° C. After a week the slide is removed from the medium and fixed by heat. It is then stained by the Ziehl-Neelson method and examined under the microscope In this interval growth will, in many cases, have been sufficient for the bacilli to be obvious and easily detected. Unfortunately, the method is technically troublesome and in many cases the material on the slide floats off into the medium Furthermore, the risk attached to this procedure is considerable to both the bacteriologist and his technicians Other methods employing solid media have also been described, but so far none of these methods has gained general acceptance

Animal inoculation

Until the development of modern egg media, animal inoculation was a much more sensitive method of detecting *Myco tuberculosis* in pathological material than cultural methods From a large number of investigations which have been performed to compare the relative merits of the two methods, it is clear the cultural methods are now as sensitive as animal inoculation and the high cost of the latter would prohibit a high proportion of the investigations now usefully performed by culture In material where contamination by acid-fast saprophytes is likely, as in specimens of urine, animal inoculation is the method of choice The specimen is concentrated by either the Petroff or tri-sodium-phosphate method and the sediment re-suspended in 1 millilitre of saline solution and 0·5 millilitre injected intramuscularly into the left thigh of a guinea-pig This should be a male animal of 300 grammes weight At the end of 8 weeks the animal is sacrificed At autopsy in a positive case there must be a local caseous lesion at the site of injection with caseous lesions in the local glands, and acid-fast bacilli should be demonstrated in these lesions If the number of bacilli in the inoculum was small these may be the only lesions seen, but in the majority of positive cases there will be generalized tuberculosis.

Streptomycin and PAS sensitivity

The principle of these tests is simple. Serial dilutions of the antibiotic are made in a liquid medium favourable to the growth of *Myco tuberculosis.* Accurately measured amounts of the strain of tubercle bacilli to be tested are then seeded into these tubes and a sim [illegible] strain of *Myco tuberculosis*, the H37Rv str. [illegible] and the lowest concentration of [illegible] The sensitivity of the test strain is then reported as less, equal to, or more than the standard strain. The technique of these tests was described by the Medical Research

Council (1948). More recently attempts to accelerate the results of sensitivity tests by incorporating known concentrations of streptomycin in solid media have been made These streptomycin-containing media are inoculated directly from the sputum and are used for primary isolation The great advantage of these solid methods lies first in their rapidity and also in the fact that these tests provide information concerning the proportion of resistant strains to sensitive strains in the bacterial population (Bradley and his associates, 1950)

Pathological material

The value of these laboratory investigations may now be briefly considered and the most convenient method is to consider them in relation to the pathological material to which they are applied

Sputum

The material most frequently examined in cases of suspected or proved pulmonary tuberculosis is undoubtedly sputum The first problem is the proper collection of a suitable specimen If possible the specimen should contain little saliva and should be free of food particles. The early morning before breakfast is the best time to collect such a specimen and the patient should be provided with a clean, dry, wide-mouthed sterile container If the patient has not previously been diagnosed this specimen should be examined by a direct film for microscopy and whatever the result of this examination the specimen should be concentrated and cultured for *Myco tuberculosis* Unless the first specimen shows many acid-fast bacilli in the direct film, this specimen should be followed by 2 further specimens which will also be put up for culture if the diagnosis of pulmonary tuberculosis is considered likely on clinical grounds If these 3 specimens should prove negative on microscopy, it will be necessary to repeat the test at frequent intervals until either a positive result is obtained or some diagnosis other than tuberculosis is established In any event, the wisest course at this stage is to persist in cultures until a positive result is obtained, especially if there is any likelihood that chemotherapy will be instituted or any possibility that the patient has contracted the disease from a patient who has been treated with streptomycin

It is customary to follow the results of a course of institutional treatment by regular examination of the sputum and, provided positive cultures of *Myco tuberculosis* are obtained at the be[illegible]

[illegible] the results of serial examinations of the sputum examined at 2-week intervals. From a [illegible]

[illegible] microscopy is no longer a sufficiently sensitive method of demonstrating *Myco tuberculosis* and vigorous attempts to cultivate the organism should be made. Sputum conversion should not be accepted until at least 3 consecutive negative cultures have been obtained from specimens taken at intervals of 2 or 3 days. When sputum conversion occurs and the patient is discharged, further specimens

of sputum should be examined at regular intervals when the patient attends the physician Providing improvement is maintained, direct microscopical examination will once more be adequate but at the slightest sign of relapse, vigorous attempts to culture the organism should be re-instituted

Not all cases of pulmonary tuberculosis produce sputum; its absence is especially frequent in children who tend to swallow their sputum.

Gastric lavage

The stomach washings are useful material from which to cultivate the *Myco. tuberculosis* in cases of pulmonary tuberculosis which fail to expectorate.

The specimen should be taken before breakfast and there should be no delay in submitting it to the laboratory. It must be remembered that the gastric juice is strongly acid and if the specimen is left un-neutralized for more than 1 hour, it is probable that the tubercle bacilli will be killed If it is impossible for the specimen to reach the laboratory within 1 hour, 5 millilitres of 10 per cent tri-sodium-phosphate should be added to the gastric washings The presence of acid-fast bacilli in a smear made from gastric contents is not conclusive evidence of the presence of *Myco. tuberculosis.* Many foodstuffs, notably butter, are frequently contaminated with saprophytic acid-fast bacilli. It is therefore necessary to culture all specimens of gastric contents

It is not always easy to subject patients who fail to expectorate to gastric lavage The most satisfactory alternative is the laryngeal swab

Laryngeal swab

In this technique a sterile swab, moistened with sterile water, is passed with the aid of a laryngeal mirror into the larynx. The patient then coughs and any sputum in the upper part of the bronchial tree will adhere to the swab. The swab is then treated with 10 per cent sulphuric acid for 5 minutes and then placed in 2 per cent sodium hydroxide for a further 5 minutes The swab is inoculated on to Lowenstein-Jensen media and incubated in the ordinary way. Nassau (1941) obtained a positive swab from 44 per cent of 273 sanatorium patients who did not expectorate, and Forbes and his colleagues (1948) showed that the results of laryngeal swabs were as reliable as gastric lavage in out-patients

Faeces

In children the faeces may be investigated for the presence of *Myco. tuberculosis* in cases of pulmonary tuberculosis in preference or addition to the gastric lavage. This method is also sometimes used in adults but here the presence of large numbers of tubercle bacilli are more likely to indicate tuberculosis of the intestinal tract than pulmonary tuberculosis

Urine

In pulmonary tuberculosis the question of renal complications occurs with some frequency and in all such cases a thorough examination of the urine for *Myco. tuberculosis* should be made. It has been the standard practice for many years to examine 24-hour specimens which are preserved with toluol. With such specimens it is essential to allow the whole specimen to sediment for at least 12 hours and then centrifuge the sediment. This material is frequently

contaminated by saprophytic acid-fast bacilli and consequently should be injected into a guinea-pig in preference to culture

More recently the practice of using a morning catheter specimen of urine, in preference to a 24-hour specimen has been gaining ground This has the great advantage that, in the absence of secondary infection, the deposit after centrifuging may be used for both culture and animal inoculation without concentration with acids or alkalis.

Pleural fluids

Simple non-turbid pleural effusions, although most frequently of tuberculous aetiology, often contain only scanty numbers of *Myco tuberculosis* The probability of demonstrating *Myco tuberculosis* is increasingly likely the larger the volume of fluid used As these fluids often contain fibrinogen, an anticoagulant should be used, for example, 1 millilitre of 20 per cent sodium citrate If possible about 100 millilitres of fluid should be examined This is centrifuged at high speed and the deposit examined microscopically If no organisms or only acid-fast bacilli are seen, six slopes of Lowenstein-Jensen media may be inoculated If other organisms are seen the material is used first for culture of secondary organisms and then treated by Petroff's or the tri-sodium-phosphate techniques before cultivation for *Myco tuberculosis*

A small volume of the fluid should be examined for cells and in simple tuberculous effusion the lymphocytes will predominate.

Turbid and purulent fluids are treated in the same way and in these cases there is greater probability of successful cultivation

Cerebrospinal fluid

In pulmonary tuberculosis at all ages, but especially in miliary tuberculosis and in children, there is the risk of meningitis developing When the signs of meningeal irritation occur, the cerebrospinal fluid should be examined The characteristic findings in tuberculous meningitis are a clear, or slightly opaque fluid under increased pressure Characteristically the fluid clots The laboratory findings early in the disease include a raised cell count of 10–50 per cubic millimetre and more than 50 per cent are lymphocytes, though early in the disease the predominant cell may be the polymorphonuclear The protein is raised, usually over 50 milligrams per cent and the chlorides are lowered usually below 600 milligrams per cent The sugar falls, usually below 50 milligrams per cent and, apart from the finding of tubercle bacilli, this is the most consistent pathological change Acid-fast bacilli will usually be seen in the stained film

In some cases of meningeal irritation the cerebrospinal fluid will be under tension and the cell count raised, but the chemistry of the fluid remains normal Such cases have been shown to be due to local irritation from a small tuberculous lesion in the cortex, resulting in a serous meningitis Recovery may occur in as many as 50 per cent of such cases and the presence of a small number of acid-fast bacilli does not exclude the diagnosis of serous meningitis if the chemistry remains normal (Lincoln, 1947)

Tests before chemotherapy

Chemotherapeutic agents in tuberculosis have two great disadvantages, *first,*

at a variable interval after the start of treatment, the organisms in the host may become resistant to the agent ; secondly, they are toxic substances The clinical laboratory, therefore, has a part to play in detecting the onset and mitigating the results of these unfortunate complications

If chemotherapy is to be given, the first step is to be sure that the tubercle bacilli are sensitive to the antibiotic before treatment begins This step should be taken in all cases but it is more important in a patient who is known to have had a previous course of chemotherapy There are no authentic reports of patients, diagnosed for the first time, being found to harbour strains resistant to streptomycin where contact with a patient previously treated with streptomycin can be excluded. On the other hand, cases contracting pulmonary tuberculosis with streptomycin-resistant strains of *Myco. tuberculosis* by contact with patients treated with streptomycin are known to occur and will probably be found with increasing frequency For this reason in all freshly diagnosed cases of pulmonary tuberculosis, the sensitivity of the infecting strain of *Myco. tuberculosis* should be measured even if chemotherapy is not under immediate consideration. The accurate estimation of sensitivity to streptomycin or PAS takes 3 weeks after the strain has been isolated and it is not suggested that treatment should be delayed until the test is complete. Specimens of sputum for culture of *Myco. tuberculosis* should be obtained before treatment commences.

In the Medical Research Council trials with streptomycin it was found that the sputum of patients with pneumonic type of tuberculosis showed a progressive diminution in the number of acid-fast bacilli present during the first 6–8 weeks In the most satisfactory cases the sputum became free of tubercle bacilli whereas in the least favourable cases the number of bacilli present in the sputum after falling to a low level between the sixth and eighth week increased to the former or even higher level There remains an intermediate group in which small numbers of bacilli continued to be present. These changes were generally associated with the emergence of drug resistance but not invariably so It seems [illegible] example, strepto- [illegible] be made from the [illegible] amined for drug [illegible]

effort to obtain further positive cultures to make sure that it is still [illegible] this information may be of great value if it is necessary to give a second course of chemotherapy

The detection of toxic complications is largely a matter of clinical examination but as both streptomycin and PAS are excreted through the kidneys, it is clearly important to make sure that there is no loss of renal function. All patients, therefore, should have a simple examination of the urine before treatment is started If albumin or casts are present, tests for urea and non-protein nitrogen retention should be performed If these show any significant diminution of renal function, chemotherapy, especially with streptomycin, should be undertaken

with caution The dosage should be controlled by frequent estimations of the blood level for streptomycin (Mitchison, 1949) and PAS (Newhouse and Klyne, 1949) as experience shows that with a lowered renal function the blood levels can quickly reach toxic levels

Serology

Many agglutination and complement fixation tests have been devised for the serological diagnosis of tuberculosis None of these tests has the accuracy of the Wassermann reaction in syphilis and none of these tests is regarded as a useful aid to diagnosis

In 1948 Middlebrook and Dubos showed that sheep's erythrocytes suitably activated with an extract of the strain *Myco tuberculosis* H37Rv were agglutinated by the blood serum of some cases of pulmonary tuberculosis Various other workers have made investigations along these lines, each of them making minor modifications in the technique Schier (1950) used purified tuberculin to sensitize the red cells and obtained good results with tuberculous sera but had a high percentage of false positive results in normal controls While this relatively recent development may eventually provide a satisfactory test in the diagnosis of tuberculosis, there is at the present time no serological diagnostic test of proved value available

Histology

Biopsy as a method of diagnosis in pulmonary tuberculosis is chiefly associated with bronchoscopy The importance of tuberculous bronchitis as a factor affecting collapse therapy is becoming increasingly recognized For this reason bronchoscopy is becoming more and more frequent in pulmonary tuberculosis Experience shows that quite severe and typical tuberculous lesions may occur without ulceration in a bronchus which appears normal Fig 151 shows an area of the bronchial mucosa which was considered to be normal at bronchoscopy In many cases of tuberculosis, bronchial biopsy shows a chronic inflammatory reaction with oedema of the mucous membrane but no histological changes specific for tuberculosis Nevertheless, it is known that tuberculous ulceration at several points in the bronchial tree may be separated by portions of bronchi which merely show a non-specific chronic inflammatory reaction (Meissner, 1946) Any bronchial biopsy showing these changes from a known case of pulmonary tuberculosis should be viewed with the utmost suspicion

Blood picture

The most constant alteration in the blood picture in all forms of pulmonary tuberculosis is a progressive hypochromic anaemia This usually reacts well to adequate treatment.

There have been many
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only fact which emerges
cific change in the leucoc
disease may be associated with either a leucopenia or a moderate leucocytosis There have also been reports of a leukaemoid reaction in a few cases of tuberculosis.

The monocyte count is frequently raised (over 10 per cent), especially when ...sh tuberculous tissue is being formed while a raised lymphocyte count is ...quently associated with healing tuberculous lesions



FIG 151 —Bronchial mucosa showing typical tubercle below a normal epithelium. Bronchoscopic examination of this piece of bronchus was reported as normal immediately before operation

...throcyte sedimentation rate

...he erythrocyte sedimentation rate, although it is not in any way specific ... tuberculosis, is nevertheless of great value In all toxic conditions ...ch are associated with tissue destruction the erythrocyte sedimentation rate ...ised, and thus the test is no more specific than pyrexia or leucocytosis The ...hrocyte sedimentation rate is slightly more sensitive and is always raised in ...ve tuberculosis and falls as healing takes place Serial examinations are ... of great value in the control of patients suffering from pulmonary tuber...sis and a spread of the disease may manifest itself by a rise in the erythrocyte ...mentation rate before there is any other radiological or clinical evidence ... The test is also often valuable in cases where radiographs reveal a lesion ...ch is of doubtful activity and in these cases a raised sedimentation rate is ...ng evidence of activity

...e two methods usually employed in this country are those of Wintrobe and ...ergren Oxalated blood is used in Wintrobe's method This is pipetted into ...ematocrit by means of a long Pasteur pipette and the tube is then stood in a ...cal position for one hour At the end of this time the upper level of the red ... is read on the graduated scale The advantage of Wintrobe's method lies

in the fact that after the reading has been taken the blood in the tube can be "packed" by centrifuging the haematocrit. If the packed cell volume is smaller than normal, a correction for the increase in the sedimentation rate due to anaemia can be made by referring to an appropriate chart. The disadvantages of the method are that the tubes are both difficult to fill and to clean. Furthermore, the method requires a high-speed centrifuge which is not normally available in a clinic

Westergren's method is much more commonly employed in tuberculosis In this method 0 4 millilitre of 3 8 citrate solution is drawn into a syringe which is then introduced into a vein Blood is withdrawn until there is 2 millilitres of mixed blood and citrate in the syringe The sedimentation tube, which has an internal diameter of 2 5 millimetres and is calibrated in millimetres from 0 to 200, is then filled in the manner of an ordinary 1-millilitre pipette The column of blood is drawn up to the zero mark on the scale and the tube is placed to stand vertically in a rack At the end of one hour the number of millimetres through which the erythrocytes have sedimented is recorded The disadvantage of the method lies in the fact that it is impossible to correct for anaemia, but the ease of the technique more than compensates for this somewhat technical disadvantage It has been found in practice that serial readings of the sedimentation rate by the Westergren method are of very great assistance in controlling individual cases of pulmonary tuberculosis

BIBLIOGRAPHY

Baker, F J (1951) "A Survey of Sputum Concentration Methods for the Microscopic Examina-

Fort

Lem
2, 818

Lincoln, Edith H (1947) "Tuberculous Meningitis in Children with Special Reference to Serous Meningitis" *Amer Rev Tuberc*, 46, 75

nd Other Body

Proc R Soc. Med 34, 391

Newhouse J P and Klyne W

CHAPTER 16

TREATMENT OF PULMONARY TUBERCULOSIS

ANDREW MORLAND and SIR CLEMENT PRICE THOMAS

GENERAL PRINCIPLES

THE SUCCESSFUL treatment of tuberculosis depends on getting the patient into so good a state of general health that the resistance is raised, the lesions first ceasing to increase, then becoming quiescent and *finally arrested and surrounded* by a dense zone of fibrous tissue For this purpose rest, fresh air and good feeding are essential

Rest

Active pulmonary tuberculosis needs months rather than weeks of bed-rest as a preliminary As a guide to progress pulse rate and temperature should be taken four times daily As slight rises in *temperature are important in the disease*, recording must be accurate Rectal temperatures are more reliable than those taken orally, after 3 minutes the temperature should be below 98° F. on awakening and should never exceed 98 6° F Mouth temperatures require 5 minutes with the thermometer under the tongue and the mouth closed, they are slightly lower and more variable than rectal The blood sedimentation rate should be done monthly, by the Westergren method and should be under 8 millimetres in 1 hour *for men and under 10 millimetres for women* *Patients with pulmonary tuber*culosis are not ready to get up as soon as the temperature is normal and even a normal sedimentation rate is frequent with a slightly active and progressive lesion For the majority the initial period of rest has to be carried out at home and most cases respond to it if social conditions are satisfactory An attempt must be made to provide early institutional treatment for cases requiring urgent collapse therapy and for those whose home conditions do not allow the patient to get adequate rest, *fresh air and food* *With overcrowded households proper* rest is impossible When an open case has to be treated at home any children should, if possible, be removed, as it is only in well-to-do homes that adequate facilities for segregation exist, some local authorities have schemes for boarding-out contact children and such arrangements are valuable in the prevention of infection

For most early cases treated at home the patient may be allowed up for *toilet* purposes; febrile cases need strict bed-rest and *absolute* or "*typhoid*" *rest* may be required for those with marked toxaemia but few can tolerate the restrictions involved for a long period. Apart from the small proportion of patients who can afford a nurse in their homes such cases require hospital treatment

After a variable period of bed-rest the time comes when the patient may start to get up, this has to be done very gradually and he should be encouraged to save effort as far as possible; for instance shaving should be done sitting instead

of standing A useful maxim is "never stand when you might sit, never sit when you might lie down" When promoted to stairs these should be taken slowly and not more than once a day at first. It is at this stage that we must be on the look-out for over-compensation ; most patients by this time are feeling [illegible]

has been done

Rest in the garden and gentle walking exercise follow, the patient being warned of the danger of sitting in the sun if the weather is at all hot Spring and autumn sun and the early morning summer sun in the British Isles are rarely harmful but in the Alps even the winter sun may produce dangerous focal reactions in active or recently active lesions During the period of gradually increasing exercise it is much better for the patient to be in a sanatorium as the necessary medical supervision is impossible in the home. With city dwellers the advantage of removal to a sanatorium at this stage is still greater, when such a patient is unable to obtain a vacancy it is better for him to continue to rest by an open window rather than to increase his exercise too quickly in order to reach a park

Fresh air

Fresh air is beneficial to the febrile patient as it diminishes night sweats. The majority of patients can be gradually accustomed to having their windows wide open day and night and only closed during the morning and evening toilet In severe weather, windows may be partially closed Elderly and bronchitic patients may not stand this hyper-aeration and are better with less rigorous treatment. The good effect of fresh air in pulmonary tuberculosis was conclusively proved by Otto Walther in his sanatorium at Nordrach in the Black Forest. It was later confirmed at the Brompton Chest Hospital which was originally designed with permanently closed windows and warmed air supplied in flues on the theory that draughts were bad for consumptives. The opening of the windows in certain wards soon demonstrated the benefits of fresh air as the appearance, appetite and general well-being of the patients so treated contrasted in a striking manner with the condition of those in adjacent wards following the older method

Climate

Fresh air can be obtained in any temperate locality, the only climates definitely bad for cases of tuberculosis being those with high temperature and humidity. During the period of bed-rest patients treated in London hospitals do not appear to make less rapid progress than those treated in the country, but when graduated exercise starts there are considerable advantages in large gardens and open country

Climate is of relatively small importance in treatment but other things being equal there are advantages in localities with cool dry air, porous soil and shelter from strong winds.

Treatment in the high Alps is rarely the deciding factor as regards recovery, in fact the more frequent respirations and higher metabolic rate make the climate unsuitable for the early toxic case. The advanced case, with dyspnoea at sea level, can only expect to be made worse by the change On the whole it is best

for sanatorium treatment to be started in the British Isles; if after some months improvement has been made but the patient is not yet fit for return to normal life, a winter in the Alps with its more pleasant and sunny climate may accelerate progress, but it need not be looked on as in any way necessary and there are advantages in curing in the climate in which the patient has to continue to live

Warm, dry climates such as South Africa, Australia, Madeira and the Canary Islands may be useful in chronic cases complicated by bronchitis. The climate of the French and Italian Riviera is a treacherous one in winter, being subject to sudden falls in temperature in the early afternoon; it is best in spring and autumn

Sanatorium treatment

Originally sanatorium treatment meant supervised exercise and rest, fresh air and over-feeding It is now coming to mean a chest hospital where various forms of collapse therapy and chemotherapy can be applied by experts at the most opportune moment. There is a need for both types of treatment. The sanatorium has considerable educational value, the patient learning how to live healthily and forming the habit of taking regular rests of about 1 hour before the principal meals, given about midday and 6 p.m The easy access to a physician who has made a special study of tuberculosis is also an advantage, as it is necessary for the patient to arrive at a considerable understanding of his disease because he will not always have an expert at hand to guide him.

Exercise is graduated by the physician, the present tendency being to avoid temperature reactions by increasing the amount of exercise slowly; it was formerly the practice to allow convalescent patients to graduate up to quite heavy manual labour and the temperature reactions resulting, attributed to *auto-inoculation* with tuberculin from the patient's own lesions was supposed *to be beneficial* These reactions sometimes resulted in a relapse and it is now thought better to avoid strenuous physical exercise for a year or two after the lesion has ceased to show signs of activity.

Occupational therapy has now become an essential part of the treatment in a well conducted sanatorium, the type of work and its duration being graded according to the patient's condition Great improvement in morale has resulted from the innovation as prolonged inactivity of mind and body is not a healthy state and only a minority of patients can profitably occupy months of bed-rest by purely intellectual pursuits Art therapy is also of great value, creative effort being particularly satisfying to a surprisingly large proportion of patients.

Village settlements

The object of sanatorium treatment is to return the patient to his former

"good chronics," who cannot be sent back to their jobs without [illegible] selves or their associates, village settlements on the lines of Papworth and Preston Hall are of great advantage As the workshops are part of the sanatorium, home life becomes possible again for married "colonists." With medical super-

vision of working conditions and hours of work the risk of relapse is greatly reduced Some effort is also made in village settlements to teach remunerative work to younger patients but up to the present there has been much greater difficulty, for financial reasons, in training young workers than in employing patients who are already skilled craftsmen and whose economic value to the settlement is on that account higher

DOMICILIARY TREATMENT

The prevalent shortage of sanatorium and hospital beds has, of necessity, forced the development of an organized system by which many of the most modern advances in treatment have been made available to patients who have to be treated at home *Para*-aminosalicylic acid being taken by mouth, lends itself easily to domiciliary treatment The practicability of giving streptomycin in the home varies with the neighbourhood as the daily injections required involve the expenditure of a considerable amount of time by district nurse or doctor As regards collapse therapy, pneumoperitoneum can be carried out quite effectively in the home, the patient being brought to the clinic by car or ambulance in most cases Phrenic crush can also be done at chest hospital or sanatorium without requiring a bed Certain clinics have also attempted the induction of artificial pneumothorax on a domiciliary basis but the need for thoracoscopy and the frequency of pleural effusions in the early months of treatment have convinced the majority of chest physicians that this form of therapy cannot be carried out adequately unless the patient can be hospitalized for at least a month

In dividing the insufficient number of available institutional beds among the long waiting list priority must be given mainly to two groups (1) those whose lives depend on prompt hospitalization , and (2) those whose homes do not permit proper segregation from children or adolescents

THE MIND

The spirochaete and the cancer cell pursue their lethal course irrespective of the previous good health of cells they encounter ; with the tubercle bacilli conditions are different Here we have a ubiquitous germ which can only with difficulty establish a bridgehead in its host , most of its invasions are repelled and even when the landing is successful if it is met by a determined resistance, the invaders are checked and finally incarcerated in successive layers of fibrous tissue ; in this prison they remain alive for many years and may profit by any lowering of resistance to escape and again produce active disease

Resistance is thus the determining factor of life or death in most cases and its precise nature needs careful analysis Physical causes, in particular nutrition and hygienic living, have been seen to play an important part in the aetiology of tuberculosis but resistance depends on the well-being of the whole organism and not merely of the body Those who are happy in their work and in their personal relations rarely provide a fertile soil for the tubercle bacillus, even when they work long hours and rear large families It is among the maladjusted that we find most cases , the alcoholic

" Who looks into a pewter pot
To see the world as the world's not "

is seeking an escape from reality to the detriment of his health, as also are those needing the distractions of a hectic night life and even, to a much slighter extent, the cigarette addict and the man or woman of overweening and misdirected ambition

The importance of psychological causes in tuberculosis has long been recognized; Laennec reported an extreme case of a strict order of nuns whose convent was several times emptied by tubercle in the course of 10 years, an occurrence he attributed less to the fasting the inmates underwent than to the policy of dwelling excessively on the more horrifying aspects of religion.

It is a curious fact that tuberculosis begins its serious ravages when the body is physically at its best, growth being finished, and that it continues to exact a heavy toll throughout early adult life only diminishing in its incidence when the cells of the body are showing the effects of the wear and tear of life That the incidence of tubercle is closely connected with the emotional disturbances of sex life is further suggested by the large proportion of cases in which there is a history of anxiety, conflict, disappointment or frustration of this origin Victorian novelists often described the jilted girl "going into a decline," such girls still do although less frequently than their grandmothers

Although any type of person may get tubercle there does appear to be a particularly high incidence among people of genius; from this has arisen the theory that the toxin of the tubercle bacillus stimulates creative effort. This theory does not bear close examination and it seems more likely that the intensity of feeling and thought required for creative work so often allied to an acute sensitiveness or vulnerability towards the inevitable harshness of a workaday world make the genius a particularly easy victim to tuberculosis. "Thought was intense with him and seemed at times to assume a reality that influenced his conduct and I have no doubt helped to wear him out." These words were written by an intimate friend after the death of the medical student poet Keats

In the long struggle between bacilli and resistance that is the case-history of tuberculosis, proper co-operation between physician and patient is essential and it cannot start too soon

When a doctor makes a diagnosis of tubercle he must realize the devastating effect the knowledge will have on his patient, it means at best a long illness, the job may not be kept open or may be unsuitable, with others, training for a career is interrupted, with the majority of married men there is the certainty of a fall in social conditions and consequently anxiety as to the fate of wife and children; with women anxiety about the home is frequently even greater Single men have less worry about their responsibilities but in some ways the blow to the basis of their personality is a greater one as there are fears that they may never have wife or family With single women, even when there is no conscious desire for children, the possibility that normal married life may be impossible is rarely borne with equanimity Although it may be necessary with a febrile patient to postpone telling him the diagnosis, it is not justifiable to keep him long in ignorance When breaking the news to the patient the doctor should naturally stress the curability of phthisis but should, at the same time, insist on the necessity for sustained effort on the part of the patient and should avoid the easy escape

of telling him that 3 months in a sanatorium will cure him completely as this will be bad for the patient and unfair to the sanatorium physician who will have to deal with his discouragement when the too favourable prognosis fails to materialize

It is not surprising that many patients refuse at first to accept the diagnosis of an illness which affects their lives so intimately Some, while verbally accepting, fail to adapt themselves to the realities of the situation and are outwardly confident that they will be perfectly well in an unreasonably short time Others show extreme shock and fear and can only gradually be brought to a more reasonable outlook On the whole the best patients are those who start with a brisk haemoptysis as they do not argue about the diagnosis and have had a sufficient fright to become co-operative patients at an early stage

During treatment

"No fool ever recovers from phthisis" was a saying of the last generation By fool we mean psychologically ill, as it is not normal through one's own carelessness to sacrifice health and even life We make great demands on the tuberculous patient which he cannot always fulfil, he should have infinite patience and at the same time show a combination of courage and caution, adaptability to a new environment and capacity to form fresh interests when the old ones are inadvisable The long strain of tuberculosis tends to bring out the essential qualities of the patient's personality in a similar way to war, even such traits as fussiness or pomposity are exaggerated The strain on marriage is considerable, many brittle unions break, but where there is true sympathy and understanding the bond becomes stronger

Home or sanatorium

Nobody likes the idea of going to a sanatorium, some even refuse to go, but most are happier when they have settled in than they were before going At home the tuberculous patient has no proper place in society, he can neither join in work nor play and his sense of being an outcast is exaggerated by the fears of infection, real or imagined, of his friends and relations In a sanatorium he enters a new society in which he can play a part and where all are in the same boat He can also learn new rules of living and with the medical guidance provided he can obtain that knowledge of the disease and its cure which it is essential for every patient to have If special methods of treatment such as pneumothorax or thoracoplasty are necessary it is important that their object should be explained to the patient as simply and clearly as possible

CHILD-BEARING IN TUBERCULOSIS

The belief that pregnancy is an almost certain catastrophe in the life of a tuberculous woman is widely held both in the general public and in the medical profession Recent work (Cohen, 1946) fails to confirm that, in general, pregnancy has any appreciable influence on the course of tuberculosis in either direction A patient with progressive disease is often better during pregnancy but is likely to relapse in the puerperium thus reaching approximately the same state in her downward career as she would have done had she not become pregnant Quiescent and

by pregnancy or parturition Obstetric compli-
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sks do not appear to be great
d-bearing is the strain involved in many
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the mother's relapse. In
some women seem to thrive on child-bearing and look
others find much greater difficulty in standing up to the strains and anxieties of motherhood.

Termination of pregnancy

Termination of pregnancy should not often be needed in tuberculosis In early active cases pregnancy does not contra-indicate either chemotherapy or
In more severe lesions, in which major surgery is likely to be
as the continuation of pregnancy would
the patient

tal capacity,
to health
active cases who have
When termination
ighth week ; after the
is required
twelfth week it is usually safer to

The provision of domestic help is the most useful measure during and after pregnancy in a tuberculous woman The infant should be inoculated with B C G as soon after birth as possible. Breast feeding is usually permissible in inactive cases and with quiescent lesions in which the general condition is good. It is naturally contra-indicated in active disease which calls for separation of the child from the mother until the lesion is under control

DIABETES AND TUBERCULOSIS

Diabetes has long been known to favour the onset of tuberculosis and the lesions found present a high proportion of the acute "adolescent" type in which there are caseous pneumonic patches not infrequently in the lower lobes

A perfectly balanced diabetic probably has as good a resistance as a normal person ; the first indication is therefore to control the diabetes if necessary with insulin and on a diet, for the tuberculosis, of about 2,500–3,000 calories The necessity for keeping balanced must be impressed on the patient , as unfortunately few diabetics are careful all the time, an increased tendency for relapse to occur must be assumed and the lesions treated with more bed rest and more energetic special measures than would be employed in a normal subject. A constant watch must be kept for fresh foci either in the lungs or elsewhere The patient's insulin requirement is a guide to the activity of his tuberculosis, as the disease becomes quiescent his requirement falls while any increase in activity is accompanied by a rise in the insulin requirement.

SPECIFIC TREATMENT

Tuberculin

More than half a century of experience has left the therapeutic value of thi

preparation doubtful, whereas there is no doubt that, if carelessly used, tubercul easily re-activates a quiescent lesion. If it has any place in medicine it is in rare type of productive lesion which tends gradually to extend in spite of goo general health, it is possible that in such cases a carefully graduated course o tuberculin will increase the patient's resistance and prevent further spread

Gold salts

The thiosulphate of gold (Sanocrysin) was used extensively some 25 years ago and some observers reported good results particularly in the exudative type of lesion, others denied any therapeutic activity. This controversy is now of purely academic interest as the arrival of streptomycin has left no place in therapy for gold salts

Streptomycin

Streptomycin, *p*-aminosalicylic acid, thiosemicarbazone and the other antibiotics are discussed in the chapter on Chemotherapy

SYMPTOMATIC TREATMENT

Cough

If severe and unproductive, cough will retard progress by interfering with rest and if lozenges are ineffective a linctus should be supplied Sometimes the mild linctus scillae may be sufficient, but in intractable cases diamorphine will have to be used

A productive cough in which the sputum is too tenacious to be easily expectorated is aided by the following taken in 2 fluid ounces of boiling water 1 hour before meals

Sodium bicarbonate	10 gr	0 6 g
Sodium chloride	4 gr	0 25 g
Spirit of nitrous ether	5 min	0 3 ml
Aqua anisi destillata (*B P C*)	½ fl oz	15 ml

Fever and haemoptysis

Antipyretics only occasionally add to the patient's comfort on account of the severe sweating produced

The most effective treatment of night sweats is hyper-aeration combined with light and porous bed-clothes Zinc and belladonna pill occasionally helps

Haemoptysis, the most dreaded symptom, if not immediately fatal, usually stops spontaneously although it may be followed by spread of disease by aspiration of infected blood clots Bleeding nearly always takes place from a cavity and is an additional reason for pneumothorax treatment which is the only effective means of preventing recurrence The use of cold food, ice-packs on the chest and calcium salts are time-honoured and being harmless are often advisable as the condition, if severe, is so alarming to patient and relatives that medical inactivity, however masterly, is unappreciated

While the bleeding continues the patient should lie with the good side uppernost to avoid aspiration, if agitated he should be given morphine which reduces seless coughing The drug should not be continued unnecessarily as it retards e clearing of blood clots from the bases

Indigestion and loss of weight

Digestive disturbances are common in phthisis and, being toxic, symptoms usually respond to rest and simple alkaline and acid mixtures. In some cases the cause of the dyspepsia is found to be milk which should first be tried citrated and if that is ineffective it should be reduced in amount or eliminated from the diet. Cod-liver oil is useful for patients who are underweight and who can digest it, but many tuberculous patients have a dislike for fats and an inability to digest them, so that they are better on a diet consisting mainly of carbohydrate and protein supplemented by vitamin tablets. The vitamin most constantly deficient in the blood is vitamin C.

The most rapid way of causing gain in weight is by means of insulin, 10 units 6 times a day being balanced with the appropriate amount of carbohydrate For the treatment a good digestion is necessary although most of the weight gained tends to be lost in a few months.

Diarrhoea

Diarrhoea is common and distressing in many advanced cases with intestinal ulceration The treatment most likely to be effective is streptomycin or in cases in which this has lost its effect the *intravenous injection of calcium gluconate.*

AFTER-CARE

Although the great majority of early cases and a considerable proportion of the more advanced ones appear to be in excellent health after a few months in a sanatorium it is well known that if a careful follow-up is made a depressingly large number will not be well and working after 5 years There are some who believe that it is in the nature of the disease for relapse to take place but I do not think such a defeatist attitude justifiable in view of the comparative rarity of relapse during sanatorium treatment, even when this is prolonged over several years An unsuitable environment after leaving the sanatorium is much more frequently the cause of disaster

As the study of the aetiology of the disease has shown, surroundings which lower the general health are more important than infection, it is a natural deduction from this that if the patient returns, with his disease quiescent but not arrested, to his previous environment, those factors which produced the original disease will not be long in starting a relapse Sanatorium experience has shown that by raising the level of the general health active lesions become converted in course of time into fibrous scars, but this process is a gradual one and few patients *remain in a sanatorium long* enough for their lesions to be surrounded by more than a thin shell of fibrous tissue, it must be the aim of after-treatment to maintain *the general health at so high a level that fibrosis continues steadily,* so that after a few years the lesions are sufficiently firmly encapsulated to stand the strain of normal life This object, the maintenance of the general health, should be achieved with no more interference with the patient's life than is absolutely necessary

The mode of life of each individual patient needs to be studied carefully in conjunction with the state of his lungs Hours and conditions of work, diet,

exercise and amusements require thorough investigation before the first problem can be solved, this is "Can the patient so modify his former life that he can reasonably be expected to keep well or must he throw up his job and learn a more suitable one?" Unless there is strong evidence that no changes that can be made will materially improve the patient's environment he should not be pressed to change his employment Work with which a man is familiar is less strain and more remunerative than starting something else as a novice

Working conditions

We have all of us heard of men who, stricken with consumption in their youth, have migrated to the great open spaces of the world, where the air is like champagne, and have cured their disease by leading the healthy outdoor life of the farmer Such people are more common in fiction than in real life, but the idea has fired the public imagination and many patients think they would have more chance of keeping fit if they gave up some sedentary office job and followed the plough. There are admittedly certain misfits in indoor jobs for whom tubercle provides a welcome means of escape to a more congenial occupation, but for the average sedentary worker to throw up his job and go in for farming is generally disastrous Not only is the work physically exhausting, but considerable skill and experience are needed It is hard enough for the farmer whose whole life has been spent in learning his job to make a living, and the majority of healthy amateurs who take up agricultural work fail to make a success of it, and financial anxiety is, in itself, a common factor in producing relapse in the tuberculous Poultry farming is more suitable than other kinds of farming as less physical exertion is needed, at the same time it is a skilled trade and to be successful needs long hours of work and considerable ability

Most indoor workers will stand a better chance of keeping fit if they carry on doing the jobs they are used to, in such cases medical advice will consist in first of all discovering whether any hygienic defects are present and if so how they may be remedied Start at the beginning of the day and find out how long it takes a man to get to his work and how he has to travel In large cities such as London many people spend 2 or 3 hours a day in crowded trains and buses getting to and from their work Some of them feel that the air they breathe in their dormitory suburbs is so much superior to that of the more central parts of the City that the difference makes the journey worth while I am convinced that many people are mistaken in this belief and would have a better chance of keeping well if they lived nearer their work The wear and tear of so much travelling is considerable and the time thus spent could be made better use of either for rest or recreation.

Ventilation is another important point, unfortunately few employees can control this; but when a man is his own master as regards the opening of his office window he should be encouraged to do so Rest hours are also difficult to continue after the patient has returned to work, but wherever possible the mid-day meal should be adequate and not the bun and cup of tea so popular with young women office workers A short rest before the evening meal should be encouraged as food is badly digested when eaten by a tired person immediately on his return from work.

With factory workers it is still more important for a man not to give up his job unless absolutely necessary as he cannot expect to earn so much at a new one Employers, on the whole, are considerate in keeping jobs open for patients and, where possible, in allowing them light work after re-employment.

Registration under the Disabled Persons Act is a great advantage to many quiescent cases during the reablement period. The "good chronic" with positive sputum continues to present a difficult problem requiring special workshops so that the disease may not be passed to his associates

School-teachers are particularly unfortunate in this respect as educational authorities are rightly unwilling to re-engage them until bacilli has been absent from the sputum for at least 6 months

There are certain occupations which are unsuitable for practically all tuberculous subjects These are mainly those involving severe physical strain

Although it is important for ex-sanatorium patients to return to or take up work at which they can earn enough to be able to afford adequate nutrition and suitable housing accommodation, they should be encouraged not to attempt to increase their earnings beyond this point at the risk of breaking down A dispensary patient of one of the authors, a taxi-driver, always stops work at about 6 p.m., although the evening hours mean quicker earning he is content to do without them as he realizes that he gets tired more easily than other drivers and that he needs rest in order to keep well

Anxiety and responsibility

Prolonged unemployment is demoralizing and after reaching a certain stage in the cure a reasonable amount of work is an advantage In assessing the probable strain of any k [illegible] tant as hours of work. [illegible] a period of worry and [illegible] sudden death of the head of a firm results in a young man with inadequate training suddenly having to step into a responsible position, similarly it is not advisable for anyone to take over a job of this kind before his disease is firmly arrested A schoolmaster, for instance, would be wiser to remain a year or two longer as an assistant than to undertake the responsibilities of a headmastership before his cure is properly consolidated Naturally if the chance is unlikely to recur one has to balance the advantages of early promotion against its possible risks. Anxiety seems to be a more frequent cause of relapse than long hours of work and it is desirable that people should not be too indispensable within a few years of active tubercle A reliable understudy is a great help to men in responsible jobs, who are otherwise afraid to consult their doctor when they think they may have started a setback in case he may try to make them stop work again

It is to be hoped that the Papworth Scheme of village settlements providing employment under healthy conditions, will find many imitations, as however hard one may try there remain some jobs which just cannot be made suitable for tuberculous patients and there are also patients who can only be expected to keep well under conditions which can only rarely be found outside special institutions of this kind

Leisure

While concentrating on trying to improve working conditions it is important not to lose sight of the way in which the patient spends his leisure hours, as relapse is just as often due to amusements as to work. Late hours and stuffy rooms have to be avoided, but care must be taken not to make the patient's life a misery by too rigid restrictions Habits matter more than exceptions—and an occasional moderately late evening makes the patient feel more of a human being and less of a leper without running any appreciable risk.

Those who return from a sanatorium with their disease still active and in whom the prognosis is bad, should not be treated too strictly The chief considerations with these unfortunates, apart from preventing them from infecting others, is to make their lives as normal as their disease will allow.

POSTURE

Postural drainage, which has so useful a place in the treatment of bronchiectasis, may be of value in cases of tuberculosis which have dilated basal bronchi as a secondary complication For certain tuberculous cavities the reverse procedure, in which the position of the patient is such that the draining bronchus is in the ceiling of the cavity, has been used with benefit For example, a patient with a cavity in the apex of the right lower lobe lies on the right side of his back while the foot of the bed is raised Much patience is required in maintaining the position day and night

COLLAPSE THERAPY

Tuberculous lesions of the lung which are submitted to surgical intervention are (1) cavitated lesions, (2) bronchostenotic lesions, and (3) closed lesions commonly referred to as tuberculomas

Cavitated lesions

Cases with tuberculous cavities form at least 90 per cent of the cases submitted for surgery The role of surgery in the majority of this group is purely mechanical,

A knowledge of the factors underlying the persistence of the cavity are necessary to a proper understanding, of the necessity for, and the aim, and object of treatment

A tuberculous cavity results from the rupture of a tuberculous abscess into one or more bronchi, the contents of the cavity either being coughed up or removed from the bronchial tree by the ciliary action of the bronchial mucosa As a result of the abscess and its rupture, a defect is left in the lung tissue which is lined by tuberculous granulation tissue, and at the same time the bronchi draining the

process affects only the submucosa, which even more proximally shows a considerable increase in its vascularity. This affection of the mucosa and submucosa

leads to a narrowing of the bronchus, variable in degree in different cases, but in all cases quite appreciable. This narrowing of the bronchus or bronchi is the crux of the whole position. *It is known that during inspiration the bronchi lengthen and the lumen of the bronchi is increased, and during expiration the reverse happens, the bronchi shorten and the lumen decreases.*

In the pathological conditions associated with a cavity, during inspiration the cavity walls are subjected to the inspiratory pull and the volume of the cavity increases, air being drawn in through the draining bronchi which have also increased in diameter. During expiration the thorax contracts, the cavity gets smaller and air is expelled from the cavity, the bronchi, during this phase get smaller, owing to the narrowing of the lumen resulting from the tuberculous bronchitis, the draining bronchi closing before the end of expiration, with the result that air is trapped in the cavity.

Trapping of air in the cavity as a result of the expiratory stenosis is the cause of its persistence. Were there a free bronchial lumen during the whole respiratory phase then the cavity would close as a result of the normal elastic retractility of the lung, as it does for example in an acute lung abscess, when free bronchial drainage is present.

Resulting from trapping of air in the cavity, a mean positive pressure is set up, on full inspiration it is negative, but during expiration the pressure becomes positive. These observations are based on pressure readings obtained while needling such cavities; in fact *a tuberculous air-containing cavity is a tension cavity from its inception. The term tension cavity is used by some authors when* referring to cavities which give radiological evidence of a relatively rapid increase in size, these preferably should be called distension cavities. The positive pressure has an added effect, it embarrasses the circulation through the capillary bed in the wall of the cavity, and in consequence the local defence mechanism is impaired. Thus the expiratory stenosis not only leads to persistence of the cavity but also to persistence of the disease itself in the cavity walls.

If the above theses be accepted, then the aim and object of treatment should be the elimination of the inflationary element in the cavity. Theoretically this can be done either by eliminating the expiratory stenosis, or by decompressing the cavity from outside, or by preventing air from going into the cavity.

The first alternative, elimination of the expiratory stenosis or in other words producing free bronchial drainage entails, certainly in the early case, a disappearance or healing of the tuberculous bronchitis. This undoubtedly happens in some cases treated with streptomycin, as would be anticipated from experience with the drug in tuberculosis of the larger bronchi, which are under bronchoscopic visual control. It is doubtful, however, whether this ever happens in the untreated case except rarely in the relatively advanced stages of the disease. Decompressing of the cavity is carried out as a therapeutic measure, either by [illegible] drainage of the cavity. The cavity, however, [illegible] However, inspection [illegible] ge shows the changes occurring, from the inert greyish walls seen in post-mortem specimens, to walls which are red and vascular, this latter stage being reached about 1 month

after drainage has been established. It is interesting to note that tubercle bacilli disappear from the discharges at about this period The third alternative, prevention of air entering the cavity, is brought about by producing a functional stenosis of the bronchus during the whole respiratory phase, the functional stenosis becoming permanent in those cases in whom a satisfactory result is obtained

This functional stenosis can result from either passive or active relaxation.

Passive relaxation

This is brought about by bed-rest, during which time the patient's oxygen requirements are at a minimum and in consequence the respiratory excursion of his chest is small. If the degree of expiratory stenosis is such that the bronchus remains closed not only during expiration but also during the small modified inspiratory phase, then further air is unable to enter the cavity, the contained air is absorbed, the tension within the cavity decreases and in consequence the blood supply to its walls improves If these conditions are maintained until the stenosis becomes organic, then the cavity closes and if the patient's resistance against his disease is good, the lesion heals and becomes arrested

Intermittent bed-rest, for example, 20 hours bed-rest and 4 hours exercise, defeats its own object, as during the exercise period, the bronchus reopens and the cavity persists It can be argued that the reverse occurs in that as a result of bed-rest, the oedema in the bronchial wall decreases and the tuberculous bronchitis improves so that the lumina of the bronchi become patent during the whole respiratory phase and cavity closure ensues.

Active relaxation

Artificial pneumothorax affords the best example of active relaxation. This intervention will be described on page 390, and the following observations only are necessary First, if the artificial pneumothorax is perfect, that is without adhesions, a cavity closure rate of about 90 per cent can be expected Secondly, the effect of such an artificial pneumothorax is to allow the lung to relax concentrically towards the hilum, and thirdly, that there is a further decrease in both the length and diameter of the bronchi.

It is logical to suppose that if the cause of the persistence of the cavity, that is partial bronchostenosis, be admitted, that the prime factor in cavity closure is closure of the draining bronchus This principle of adequate relaxation underlies all the operative interventions of this group, the principal factor being the elimination of the inspiratory pull on the bronchus, allowing the closed expiratory position of the bronchus to be maintained throughout the whole respiratory phase

Some workers maintain that the effect of artificial pneumothorax is to straighten out a previously kinked bronchus, the latter being the cause of the persistence of the cavity, and as from this straightening, free bronchial drainage results, the cavity closes This thesis fails to give cognizance to the observation that bronchi normally get narrower when an artificial pneumothorax is induced, and if it is admitted that a partial bronchostenosis be the cause of cavity persistence, then it is reasonable to suppose that the former explanation is possibly the more correct

Houghton has pointed out that massive atelectasis usually leads to disaster, pleural infection and contralateral spread being a frequent sequelae, and argues thus that bronchial occlusion instead of being beneficial in the closure of cavities is harmful This cannot be accepted unreservedly It is correct that atelectasis from any cause constitutes a handicap to the patient if only on physiological grounds The significance of massive atelectasis, that is lobar or multilobar, is an index of widespread involvement of the mucosa of the bronchial tree and can equally be taken as an index of the patient's poor resistance against his disease; superimposed on this is the severe interference with the vascular bed in the atelectatic lung which limits the local defence mechanism in the affected area and predisposes to extension, often rapid, of the disease process. Houghton in noting that cavities in atelectatic lobes often persist, uses this observation to controvert the theory that occlusion of the bronchi draining the cavity does not lead to cavity closure This conclusion seems attractive at first, but on careful examination, it appears that the so-called bronchial occlusion cannot be complete because the cavity is air filled, and in some cases can be seen to balloon in the atelectatic lobe, evidence in itself that the lumen of the cavity is still in communication with the bronchial air stream, and there is probably still an expiratory check valve action in the bronchus

Whichever of the above conceptions is correct it is agreed that concentric relaxation of the lung gives the highest rate of cavity closure in those cases that will not close by conservative means, that is bed-rest or chemotherapy, or a combination of the two

Surgical interventions employing the principle of relaxation are (1) artificial pneumothorax, (2) diaphragmatic paralysis with or without pneumoperitoneum, (3) extrapleural artificial pneumothorax, and (4) thoracoplasty

ARTIFICIAL PNEUMOTHORAX

Introduction of air into the pleural space relaxes and partially collapses the lung, as may be seen on the x-ray screen, respiratory movements continue but to a diminished extent The induction of an artificial pneumothorax is simple and, if certain elementary precautions are observed, almost devoid of risk; refills are even more easy and safe In so much simplicity there lies considerable danger as the selection of cases and the choice of time call for great care and considerable experience, and the management of an artificial pneumothorax requires constant vigilance if the best results are to be obtained

Indications and contra-indications

Pneumothorax treatment is indicated in the following types of case:

(a) Unilateral cavitation—however small

(b) Non-cavitated lesions with positive sputum

It must be kept in mind that histological examination of a lung may show giant cells, caseation and cavitation in a lesion less than 1 millimetre in diameter and therefore quite invisible on an x-ray film An infiltration with positive sputum probably means cavitation; in such cases a preliminary period of bed-rest, perhaps combined with streptomycin and *para*-aminosalicylic acid should be

prescribed in the first place, the decision to do an artificial pneumothorax later depending on the patient's progress, home environment and work. Poor progress and unsatisfactory social conditions are indications for collapse therapy in such cases

(c) Non-cavitated lesions without tubercle in the sputum *Artificial pneumothorax* is only indicated if such lesions tend to spread in spite of general treatment

Tuberculous laryngitis is an indication not only for streptomycin but for cavity closure to prevent reinfection Diabetes is an additional reason for active treatment

The types of case in which this treatment is contra-indicated include ·

(a) Fresh, caseous lesions in a highly active state may give excellent immediate response to pneumothorax treatment, but the risks of tuberculous empyema, atelectasis and distension cavities are so great that preliminary treatment designed to reduce the degree of activity is essential Bed-rest, streptomycin and *para*-aminosalicylic acid, pneumoperitoneum and phrenic crush should be used in the first place, after several months artificial pneumothorax will prove suitable in a considerable proportion of these cases, in others destruction of the lung will be found so extensive that resection or thoracoplasty after a longer delay will give a better chance of arrest.

(b) Tuberculous bronchial stenosis is an absolute contra-indication to artificial pneumothorax treatment Bronchoscopy is indicated wherever this condition is suspected

(c) Fibrotic apical lesions with cavitation and contraction give much better results with thoracoplasty than with artificial pneumothorax In such cases collapse, if obtainable at all, is nearly always contra-selective, adhesions are difficult, dangerous or impossible to divide and it is better to prepare the patient for surgical treatment in due course rather than to expose him to the additional risks of an artificial pneumothorax which will almost certainly be ineffective

Provided the vital capacity is adequate an active lesion in the better lung is no contra-indication

Age—Artificial pneumothorax treatment is well tolerated in adult types of phthisis in children Elderly patients tend to stand collapse therapy less well In this age-group fibrotic forms of disease are more common; not only are they less amenable to artificial pneumothorax treatment but vital capacity is reduced and cardiac strain correspondingly increased Careful assessment of such factors is required in patients between 50 and 60 years of age and above the latter age indications need to be exceptionally strong to justify collapse treatment

Pregnancy—Artificial pneumothorax treatment can well be started during pregnancy but if the case is not diagnosed or not ready until the seventh month or later the operation is best postponed until after delivery.

Heart disease—Mitral stenosis, the commonest severe cardiac lesion of young adults, is rarely associated with pulmonary tuberculosis; when the two occur together collapse therapy is not contra-indicated provided compensation is good

Asthma—The pure spasmodic type of asthma with little or no lung damage does not contra-indicate collapse therapy More chronic types with fibrosis and emphysema are unsuitable subjects for artificial pneumothorax

Induction

Apparatus.—One of the siphon type of apparatus such as the Lillingston-Pearson or the more modern Stott is best for the induction. When a portable box is required the Maxwell is both convenient and reliable.

Needles—For the induction a sharp short-bevel needle either with closely fitting trocar (Kuss) or with stilette (Saugman) is to be preferred to the thick blunt Rivière type which requires incision of the skin if excessive force is to be avoided.

Position of patient.—For the induction the patient lies on the good side with 1 pillow transversely under the chest and another for the head. It is important that the affected side should be convex and well stretched. After cleansing of the skin 2 millilitres of local anaesthetic (2 per cent Novocain) should be injected first raising a small wheal (if adrenaline is used with the Novocain a slough may result) The intercostal muscles are hardly sensitive and there is no need to waste much anaesthetic in them, as the needle slowly approaches the parietal pleura a little pain will be experienced; this is the level at which at least half the anaesthetic should be given; further advance of the hypodermic needle should be painless Puncture of the lung is harmless, air and a little blood will enter the syringe on pulling up the piston. Injection of Novocain into the lung is not only useless but apt to produce coughing

Site—The usual site for induction is the third or fourth space in the mid or anterior axillary region: if the underlying lung in this part is diseased another site should be chosen.

After a wait of at least 2 minutes the induction needle should be inserted slowly, by cautious procedure it is usually possible to feel the parietal pleura, a sudden diminution of resistance indicating that the membrane has been pierced. This is the time for taking out the stilette and reading the manometer—a sustained negative swing of 5–10 centimetres of water indicates that the needle point is in the pleural space. If the layers of pleura are stuck together or if the operator has overshot the mark a pulmonary swing will occur the pressure varying about the zero mark, for example -2 $+2$ A slight negative pressure may be found just before the parietal pleura is pierced; its amplitude is always small

When a satisfactory pleural swing has been found air may be introduced gradually—the water level of the fluid in the 2 bottles should be kept the same so that air is sucked into the chest rather than being blown in It is best to keep the manometer working throughout the induction as this will warn the operator at once should the point of the needle move from the pleura Readings should be taken every 50 millilitres, provided that they remain negative 300–400 millilitres may be given A positive pressure with a smaller amount shows that a small pleural pocket has been entered, another site may be tried but the chances of a satisfactory artificial pneumothorax resulting are small

After the induction the patient should not change his position for half an hour—this reduces the incidence of surgical emphysema A sedative for the first night is usually required

Refilling

The first refill should be given the next day, the second, 2 days later after

which it is usual to take an x-ray picture management being guided by the result shown Until x-ray examination has shown the establishment of a good pleural air space, a local anaesthetic should be used and the needle inserted slowly. For subsequent refills the writer's (A M) fine solid-pointed needle with side opening has the advantage of making local anaesthesia unnecessary It must be kept sharp and dry and insertion must be rapid and intercostal

Complications of pneumothorax treatment

Air embolism

Air embolism is the only serious immediate risk ; it is prone to occur in shallow artificial pneumothoraces in which there is difficulty in finding the pleural space. Obliterative pleurisy closing the previous refill site is a common cause and should be guarded against In a lung indurated by disease the veins are held open by fibrous tissue and simple puncture of the lung may be sufficient to establish a connexion between air space and vein Embolism may also occur through the intercostal veins and follow venous anastomoses to the brain Cerebral air embolism shows itself by visual disturbance, numbness and involuntary movements of arm or leg or by loss of consciousness Should any of these symptoms occur the needle should be promptly withdrawn and the patient's head lowered. Coronary embolism may result in sudden death and is the probable cause of most cases reported as " pleural shock "

Pleural shock

When allowance has been made for coronary air embolism, idiosyncrasy for local anaesthetic, status lymphaticus and the tendency for cardiac inhibition to result after slight stimuli in the near moribund it is doubtful if there is any place left for pleural shock, that is a cardiac inhibitory reflex from the parietal pleura. It used to be taught that failure properly to anaesthetize the pleura favoured the occurrence of pleural shock but this is not true as in most recorded cases a local anaesthetic has been used whereas most refills are now given without Mediastinal displacement, due either to too large a refill or to too low a pressure with aspiration of fluid, may cause the sudden onset of auricular fibrillation with associated shock

Traumatic pneumothorax

Puncture of the visceral pleura cannot always be avoided at the induction and may also occur with a shallow pleural space Provided the portion of lung punctured is healthy the accident is not a serious one Patients should be warned to report any shortness of breath after a refill , in such cases radiographic exam- [illegible] connected with a water seal Even with a wide bore needle obstruction with serum soon occurs and frequent cleaning with a stilette is necessary The writer's (A M) tension pneumothorax apparatus has been designed to meet the principal difficulties of this grave complication

Haemothorax

Haemothorax, from puncture of an intercostal vessel is a rare complication

Blood in the pleura should be aspirated and the space washed out with sterile saline solution

Management

The rate of absorption of air through the visceral pleura is variable, and the correct spacing of injections and amount of air can only be gauged by regular screening before each refill Large infrequent refills treating the lung like a concertina are best avoided ; in an average case 2 or 3 weeks of frequent refills are sufficient to establish the optimal degree of collapse which can be maintained by weekly refills of not more than 500-600 millilitres After the first year the interval can generally be increased to 10-14 days but a considerable number of patients continue to require weekly refills for 2 or more years

In some cases, particularly in young subjects, the mediastinum is very mobile and is displaced to the opposite side before much collapse of the affected lung is obtained , such cases require small frequent refills

Since cavity closure is the main object of collapse therapy careful x-ray supervision of cavities is an essential part of artificial pneumothorax management. Pleural adhesions are frequently present and as these are due to involvement of the pleura in the disease they are most commonly attached to the lung in the vicinity of the cavity [illegible]
When thoracoscopy [illegible]
best course in most [illegible]
prepare the patient for some other method of collapse Occasionally an apparently unsatisfactory artificial pneumothorax results in cavity closure , in such cases the artificial pneumothorax may be continued but the previously excavated area should be regarded with suspicion and serial tomographs are advisable.

Relaxation of the lung usually results in cavity closure in the course of a few weeks but occasionally the reverse happens and the distended cavity projects like a balloon from the surface of the collapsed lung This situation is one of great danger as rupture may occur and the pleura become infected ; air must be withdrawn promptly, the patient put to bed and given streptomycin and *para*-aminosalicylic acid These measures may be followed by diminution and closure of the cavity before the lung is fully re-expanded and in such cases the artificial pneumothorax may be continued ; in the majority, however, other methods of collapse are necessary When cavity closure is delayed it may be possible by varying the amount of collapse to find a position in which closure takes place ; the lung should be kept in this position by frequent small refills Some cavities close when the lung is well collapsed, others only when collapse is minimal ; no hard and fast rules can be laid down, each cavity must be the subject of individual study.

Atelectasis

Sometimes during the course of artificial pneumothorax treatment, usually in the early stages, a lobe, or a portion of a lobe (occasionally a whole lung), may become atelectatic. The lobe or segment affected is usually the part of the lung most seriously diseased and x-ray examination frequently shows that although a complete selective collapse of the diseased area has been obtained the cavity

is still patent The risk of spread to the opposite lung or to the pleura is so great that this condition calls for removal of air, a procedure which often results not only in re-aeration of the lung but also in cavity closure, the artificial pneumothorax may then be continued In such cases bed-rest combined with streptomycin and *para*-aminosalicylic acid therapy should be applied with a view to clearing the blocked bronchus

Pleural effusion

Some degree of pleural effusion occurs at some time in the course of the majority of these operations Apart from certain "ex vacuo" effusions occurring with the low pressures resulting from attempts to re-expand a rigid lung, pleural effusion indicates spread of the disease to the pleura The onset of an effusion is sometimes preceded by a rise in pressure probably due to the rupture of a small subpleural caseous focus with the production of a spontaneous pneumothorax Symptoms are variable, sometimes a small puddle of fluid is a chance finding on screening in an apparently healthy patient, the onset of others is sudden and severe with grave constitutional disturbance and high fever which may last weeks or even months The fluid is clear and straw-coloured at first, most cases show an excess of lymphocytes but those of greatest severity may have the polymorph as the predominant cell in the early stages Tubercle bacilli are commonly found on direct examination in the more severe cases and those due to cavity rupture, even in cases of symptomless onset, culture methods or guinea-pig inoculation usually give a positive result

Apart from symptomless effusions of a few millilitres the outpouring of fluid into the pleural space calls for bed-rest Needling of the pleura, apart from diagnostic puncture with a fine hypodermic, should be avoided as trauma tends to increase the inflammation Refills should be avoided unless the lung shows a tendency to re-expand rapidly—it will only do this in the smallest effusions With moderate or large effusions aspiration may be required, this should not be done during the first 6 weeks unless the fluid pushes over the mediastinum and over-collapses the lung When fluid is removed an attempt should be made to bring the mediastinum back to its normal position and to induce a moderate degree of re-expansion of the lung After most effusions some degree of thickening and loss of elasticity in the visceral pleura is the rule and if the lung s left fully collapsed it is unlikely that it will ever re-expand adequately Many effusions are absorbed without aspiration, others after being removed few times, but some persist and these should be carefully watched as they are ble to become purulent

berculous empyema

After cavity rupture the effusion which forms rapidly becomes purulent; in er cases fluid which is clear and straw-coloured at first becomes increasingly dy and finally thick tuberculous pus The close connexion between atelectatic in the lung and effusion has recently been established and in many cases ema would have been avoided if more timely efforts at re-expansion of sed areas had been made In any case the attempt to re-expand the lung bliterate the pleural space should not be delayed when the fluid has become

cloudy. A variety of solutions have been used for pleural irrigation of which *Azo-chloramine-T* and *para*-aminosalicylic acid are the most popular at present but results can only be described as fair and tuberculous empyema remains a *dangerous condition* with a high mortality Pleural wash-outs which should be done at least twice weekly and the maintenance of a low intrapleural pressure (*not too low or cardiac disturbances* may result) should cause partial if not complete obliteration of the pleural space When this is only partial and symptoms of toxaemia *persist thoracoplasty is indicated*. The further the lung can be re-expanded prior to the operation the less extensive will the rib resection have to be *Thoracoplasty is not indicated in all cases of tuberculous empyema*, in some it is contra-indicated by the condition of the opposite lung, in others although a few tubercle bacilli *persist in the fluid the general condition is satis*factory, formation of pus slow and the prospect of recovery by conservative treatment good Such cases may *require aspiration at intervals of 3 to 12* months, others can be left alone completely.

Broncho-pleural fistula

Broncho-pleural fistula from a ruptured tuberculous cavity ensures infection of the pleura and prevents re-expansion of the lung Surgical treatment is required

DIAPHRAGMATIC PARALYSIS

The obvious effects of paralysis of the phrenic nerve are the elevation of the [illegible] Elevation of the diaphragm decreases [illegible], vertical relaxation [illegible]e posterior part of the apex of the lung depends on the active inspiratory descent of the diaphragm in the following way the descending hemidiaphragm, through the attached ligamentum latum pulmonis, pulls the lung root downwards and forwards, and in this way, the area of the lung, above and behind the root, is made to expand. *It is certainly* true that the degree of costal separation of this area of lung is minimal

It is conceivable that, when the lung is free within the pleural cavity there is a certain degree of uniform relaxation throughout the whole lung, but the *inspiratory pull, or its lack, is felt in the vertical direction*

Paradoxical movements apparently have no beneficial effects, rather the reverse, *certainly so, as judged by the observation* that paralysis of the diaphragm, in patients submitted to thoracoplasty, increases the risk of atelectasis of the lower lobe between 2 and 3 times The addition of a pneumoperitoneum enhances the value of diaphragmatic paralysis, not only by the increase in the height of elevation of the diaphragm, but also possibly in the decrease in the degree of paradoxical movements

Diaphragmatic paralysis is what may be termed a long distance method of relaxation, and when cavity closure follows its use, this probably results from the elimination of the inspiratory tug on the draining bronchus, the disappointing results can be explained *on the thesis that the draining bronchi are* still subject to the lateral inspiratory pull of the chest wall

Interruption *of the phrenic nerve may be either temporary or permanent*

Temporary interruption is carried out by crushing the nerve and any accessories with fine artery forceps, the paralysis lasts up to 18 months although in a small percentage of cases it may be permanent The advantages of temporary paralysis are obvious in that normal function can eventually be re-established Permanent paralysis is generally produced by evulsion of the nerve, the accessory branches being ruptured during the evulsion The operation is a simple one and without doubt has been used indiscriminately in the past The chief danger of the use of the operation in unsuitable cases, is that it gives the medical attendant and the patient a sense of false security, again it is an obvious waste of time unless a satisfactory result can be expected The increased risk of basal atelectasis if a thoracoplasty is undertaken has already been pointed out This risk can to some extent be mitigated by inducing a pneumoperitoneum before operation in order to limit the paradoxical movements of the diaphragm

Indications

The prime indications for diaphragmatic paralysis are —

(1) Apical cavitation with little or no associated infiltration and when the cavity is not larger than 2½ centimetres in diameter

(2) In association with an artificial pneumothorax for apical cavitation when the lung is attached to the dome of the pleura and to the diaphragm and there are no mediastinal or lateral adhesions

In both of these groups, satisfactory results can be anticipated in a reasonably high percentage of cases

(3) Cases with cavities in the apical and basal portions of the lower lobe generally in conjunction with artificial pneumothorax or pneumoperitoneum

The expectation of closure in this group, especially so in the basal cases, is not more than 30 per cent It is, however, a perfectly justifiable procedure in these cases as other relaxation procedures do not give much better results

In all cases in which the interruption has been temporary, it is necessary to keep the diaphragmatic movements under constant radioscopic control, in order that the nerve may be recrushed at the first sign of return of normal movements, until the paralysis has been present for such time as is judged necessary in the individual case The nerve may have to be recrushed 3 times

ARTIFICIAL PNEUMOPERITONEUM

Inflation of the peritoneal cavity with air pushes up the diaphragm and restricts the movements of respiration A pneumoperitoneum without phrenic crush causes a slight or moderate diminution of movement of both lungs, the addition of a phrenic crush causes the paralysed side of the diaphragm to rise considerably thus greatly diminishing movement of the lung on that side whereas on the non-paralysed side movement is practically normal

A pneumoperitoneum is less effective than a good artificial pneumothorax but is much better than a bad one Cavity closure, in unilateral cases, follows in about three fifths of the cases irrespective of the part of the lung affected The great advantage of pneumoperitoneum is that it may be used in highly active caseous types of disease in which artificial pneumothorax would be dangerous on

it is therapeutically useless and does not add to the patient's confidence When the operator believes that his needle has penetrated the peritoneum air should be run in slowly with a positive pressure of about 10 centimetres of water ; a small and gradually increasing positive pressure will then be recorded by the manometer. Air rapidly spreads over the abdomen and diminution of liver dullness is soon observed

Approximately double the amount of air required for pneumothorax is given, from 600 millilitres to 1 litre being usual for an induction and refills, the first after two days and subsequently weekly, of about the same amount being required The same site may be used as for the induction or this may be changed to the right side in cases in which the right phrenic nerve has been crushed as in such cases a large air bubble will be present on this side and the risk of injury to the gall bladder will have become negligible

Complications

Air embolism is much less to be feared than with pneumothorax and few cases have been recorded

Perforation of stomach, bowel or gall-bladder may occur especially if peritoneal adhesions are present but the results are rarely serious Occasionally a defect of one side of the diaphragm results in pneumothorax

Peritoneal effusion in pneumoperitoneum treatment is much less common than is pleural effusion in artificial pneumothorax treatment The presence of tuberculous peritonitis, the original condition for which pneumoperitoneum was used, is now considered a contra-indication and the development of a large effusion calls for the cessation of the treatment

Management

In cases in which pneumoperitoneum is used merely as a stage in a planned course of attack on the disease the optimum moment for its replacement by artificial pneumothorax or thoracoplasty will have to be chosen When pneumoperitoneum is the sole method of collapse therapy employed it should be kept up as a rule for 2 or 3 years When, as is usual, phrenic crush is combined with pneumoperitoneum the return of diaphragmatic movement must be watched for on the screen and the nerve re-crushed if necessary

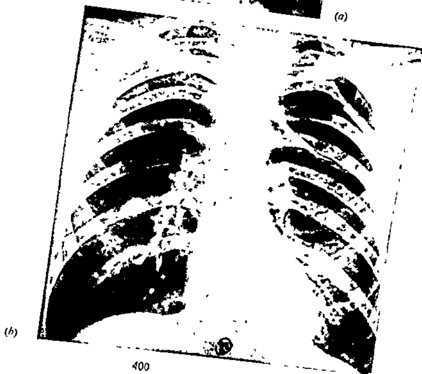
EXTRAPLEURAL ARTIFICIAL PNEUMOTHORAX

Extrapleural artificial pneumothorax is established operatively A segment of the fourth, fifth or sixth rib is resected and the pleura with the underlying lung is stripped away from the chest wall, the dome of the hemithorax and the mediastinum to the [illegible] endothoracic fascia [illegible] to the chest wall [illegible] cases the parietal pleura can be mobilized from the whole of the chest wall and the outer half of the diaphragm, resulting in complete extrapleural artificial pneumothorax

Extrapleural artificial pneumothorax thus reproduces the conditions maintaining in an intrapleural one, relative to the area of lung mobilized, in that it is concentrically relaxed (*see* Fig 152) It differs, however, from the intrapleural type,

FIG 132 — Male, aged 37 years Bilateral pulmonary tuberculosis with cavitation left side; extrapleural artificial pneumothorax. *(See Case Report C.M)*

(a)



(b)

apart from the anatomical considerations, in that the lung is not a subject to the same respiratory variations in size, because a fairly resistant membrane is formed over the pleural surface, which tends to keep the lung immobile This explains the more rapid control of toxic phenomena which occurs with extrapleural pneumothorax

Case Report C M

Male, aged 37 years

25 4 38 Admitted to hospital with history of frequent chest colds and loss of energy since autumn of 1936 March 1937, haemoptysis and was off work for 2 weeks January 1938, haemoptysis for one week with malaise and night sweats Chest radiographed and sputum examined Found to be T B positive Rested in bed until admission to hospital On admission, afebrile, general condition good, sputum ½ ounce, T B positive, continued at bed rest, gained nearly 2 stone in weight

Fig 152a Condition after admission cavity left upper zone, infiltration right upper lobe No evidence of cavitation

10 12 38 Left extrapleural artificial pneumothorax established Post-operative course smooth and uneventful

Fig 152b Condition 7 years after operation extrapleural artificial pneumothorax well established, some scattered discrete shadows in right upper lobe

27 2 49 Weight stationary, extremely well has been working full time as warehouseman

The operation has a limited application in that unless the pleura can be easily stripped away from its bed, certain complications are apt frequently to occur, the commonest being infection of the extrapleural space

The presence of a tuberculous lesion in the lung especially if superficially placed, leads sooner or later to adhesion of the visceral to the parietal pleura and if the condition is progressive, the inflammatory change involves the endothoracic fascia, *pari passu* with this latter involvement, the bronchial blood supply to the area of lung involved becomes deficient, and an adventitious blood supply from the vessels of the chest wall is established Separation of the parietal pleura from the chest wall when these conditions maintain, leads to a partial deprivation of the blood supply to the diseased area with a consequent quiet necrosis and extension of the disease process to the extrapleural space

With this difficulty in view, the operation is preferably limited to cases in whom the disease is (1) early, (2) limited to cavitation of not more than 3-3½ centimetres in diameter and (3) located to the apex If these indications are followed, good results will ensue, with greater experience of the procedure, these indications can be extended somewhat to include cavities of larger dimensions, but only exceptionally when the disease has been established for a long time

Operative complications

The complications of the operation are haemorrhage, and pyogenic and tuberculous infection

Haemorrhage

This is the most common immediate post-operative complication In all cases, there is some oozing into the extrapleural space, this being of no clinical significance Occasionally the haemorrhage is of serious proportions and rarely may be fatal The bleeding commences usually about 48 hours after operation and most commonly follows straining, either as a result of coughing, vomiting or at stool The haemorrhage often occurs rapidly, appears to be venous in character,

and most probably results from the dislodging of a clot from the mouth of a vein. The first sign of haemorrhage is most commonly dyspnoea, due to the mechanical effects of the collection of blood, collapsing the lung on the operated side, displacing the mediastinum and thus decreasing the volume of the opposite lung, and the decrease in the cardiac intake resulting from the pressure on the vena cavae Added to these mechanical effects, is the actual loss of circulating blood volume

Treatment.—The prime necessity is to replace the lost blood by transfusion. The mechanical effects are rectified by aspiration of the blood from the extrapleural space Care should be taken to perform the aspiration above the level of the pleural reflexion because unless the pleura has been stripped further by the haemorrhage, the needle may be pushed through a fringe of lung and the space may be infected. In most cases, clotting takes place and space cannot be emptied. If, after due trial, aspiration is unsatisfactory it should not be persisted with. It will be necessary to reopen the wound and remove the clot, using parenteral and local penicillin cover Failure to remove the contained clot will lead at best to partial if not complete obliteration of the space and at worst to late infection of the space.

Infection

Infection of the space may be pyogenic or tuberculous.

Pyogenic infection.—This is due to faulty technique and should not occur. If and when it does occur, it should be easily controlled chemotherapeutically, if the organisms are sensitive to the various chemotherapeutic agents at our disposal

Tuberculous infection.—The cause of the above has been discussed, and obviously prophylaxis is better than cure However even with the greatest care in the selection of cases, tuberculous infection of the space will occur in a certain percentage The infection generally comes on about 6 months after operation. The onset is quiet and recognition depends on needling the space in which a fluid level has been recognized radioscopically or radiologically The course of the disease is quiet, acute phases such as occur with the intrapleural type are notably absent ; the reason for this is probably to be found in the fact that the pulmonary lesion is better controlled in the extrapleural type, whereas in the intrapleural type, the precipitating cause of the pleural infection is the imperfectly relaxed and therefore uncontrolled pulmonary lesion

Treatment is conservative Aspiration of the space, leaving the pressure highly negative, in the large majority of cases produces in a week or two a dramatic change in the aspirated fluid which becomes sero-sanguineous. The pressures after 1 month should be left at atmospheric level and the fluid will absorb, the artificial pneumothorax then can be carried on as usual. Experience with streptomycin in this type of case is not at present sufficient to give a definite ruling, but its use in tuberculous infection in the extrafascial thoracoplasty spaces is sufficiently good to warrant its advocacy in the extrapleural cases

Post-operative care.—There are two apparently contradictory lines of treatment advocated in the post-operative management The first advocates frequent aspiration in order to keep the cavity as dry as possible up to the time when the cavity

becomes dry The other states that aspiration should be as infrequent as possible and only undertaken if haemorrhage has been suspected It has been found that the space becomes dry about 1 month following operation despite the type of post-operative treatment The advantage of infrequent aspiration is that the risk of infection is markedly decreased, either by failure in aseptic technique, or inadvertent lung damage, and it certainly seems that judging by the ultimate result, frequent needling offers no commensurate advantage When the space is well established and dry, the pressures in the space are usually left at each refill on the positive side, a mean of + 10 + 15 In the early stages, however, a mean atmospheric reading is preferable.

THORACOPLASTY

Thoracoplasty is, for the following reasons, the most serious operation used to produce relaxation of the lung

(1) The extent of the intervention, involving as it does the resection of a varying number and length of ribs with perhaps the addition of apical mobilization, constitutes a much more serious procedure than that used for the production of an artificial pneumothorax

(2) The direct result of the rib resections is that the chest wall becomes flail and the underlying lung is thus subject to paradoxical movement and it is in this latter respect that the chief cause of severity lies

The effects of paradoxical movement in this connexion are two-fold, physiological and pathological

Physiological effects

The movements of the uncovered area are the reverse of normal, in that during inspiration, air is drawn from the uncovered area into the parts of the lung which are subject to normal respiratory movements, and during expiration, air from the normal areas, not only is forced out through the trachea, but also back into the unsupported area of lung This pendulum movement of air is tantamount to increasing the pulmonary dead space, and in addition the air entering and leaving the affected area is already deficient in oxygen and has a high carbon dioxide content In essence it is the same pendulum swing of air which occurs between the collapsed and uncollapsed lung when an open pneumothorax is present Doubtless the other harmful effects of an open pneumothorax, mediastinal movements with their reflex disturbances and lack of aspiration on the big vessels leading to deficient cardiac filling and in consequence output, occur as well but in a lesser degree The severity of this interference with the cardio-respiratory reserve will manifestly depend on the volume of lung and the area of the chest wall subject to such paradoxical effects

Pathological

The other danger of paradoxical movements is the increased risk of bronchogenic spread Secretions which may be expressed from the affected area of the lung are expressed at the crucial time when the areas of normal lung are expanding Theoretically the normally expanded areas of lung are equally effected, but the contralateral lung maintains its normal cough mechanism On the operated

side, however, the expulsive effort is impaired, because the normal architecture of the chest has been interrupted by the rib resections In practice, it is the lower portions of the lung on the operated side which bear the brunt of this bronchogenic extension

Appreciation of the above factors is the main reason for performing the operation of thoracoplasty in stages, so that each intervention will liberate successive areas of chest wall and leave sufficient time between the stages to allow of a certain degree of consolidation to occur of the area previously liberated

Operative technique

The operation is done under local anaesthesia, through a J-shaped incision which roughly follows the vertebral border of the scapula, nearer to the vertebral spinous processes than the scapula itself and curving forwards below the latter's inferior angle

After reflexion of the scapula by detaching the serratus magnus from the ribs, the ribs, most commonly the first to the third, are resected. The apex of the lung is now mobilized in the extrafascial plane from its attachments to the vertebral column and the mediastinum, ideally as far as the lung root.

The second stage is carried out a fortnight later, again under local anaesthesia and through the same incision In the average case, portions of the fourth, fifth, sixth and seventh ribs are resected and further mobilization of greater or lesser extent is carried out in the costo-vertebral sulcus and if necessary on the mediastinum

The third stage if it be necessary, is done again under local anaesthesia after a fortnight's interval The lower part of the original ? is used with the addition of an oblique incision running downwards and backwards from the angle of the original one. Portions of the eighth, ninth and tenth ribs are removed at this stage.

The length and number of ribs to be taken at each stage will vary according to the condition of the patient and of the lung (Fig 153) In toxic cases, in those in which resistance against the disease is judged to be poor, and also in those cases where the lung is very soft, small numbers of ribs and lengths of resection are indicated , for example, it may be deemed wise to resect only the first and a small portion of the second rib with corresponding apical mobilization at the first stage and comparable amounts at the successive stages. Although it is true to say that from the technical point of view, it is easier to do an extensive mobilization [illegible] cannot [illegible] es of the operation are not the patient's but the surgeon's ...

When the apex is solid and firm, not only can large resections of the first, second and third ribs be taken, but also posterior segments of the fourth, fifth and even the sixth with a corresponding apical mobilization be performed, without adding appreciable risk (Fig 154) The interval between the stages is similarly subject to the patient's condition The ideal length of time between stages is a fortnight, the apex by this time is sufficiently stabilized to warrant proceeding with the operation, in a further week the tissues have become more solid but also more friable and remobilization of the apex becomes increasingly



FIG 153 — Female, aged 24 years Pulmonary tuberculosis of 2 years standing, large cavity left side partial collapse right lower lobe, left thoracoplasty (*See Case Report J.W.*)

(a)



(b)



FIG 153 (*cont*)

(*c*)

more difficult Despite these considerations, however, there is no warranty for proceeding with the next stage unless the patient's general condition will allow.

The extent of the operation should be determined on the pre-operative radiographs. As a general rule, rib resections should be carried out to include the whole of the diseased area and rib space below it The danger is usually to limit the extent of resection necessary and to leave an area of disease unrelaxed.

Case Report J W

Female aged 24 years

September 1944 Admitted to hospital with 2 years history of pulmonary tuberculosis, left artificial pneumothorax having been tried General condition fair Sputum positive Vital capacity 1,000

Right lower

terior ends of

e uneventful.

r segments of

a on running

Complications

There are certain accidents of the operation which are of general interest.

Perforation of the pleura—This is not an uncommon accident, especially so in the relatively early case, and has no serious sequel Experience has shown

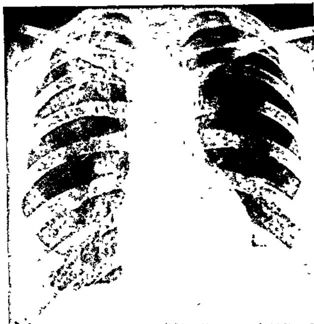


FIG 154 — Female, aged 29 years Bilateral pulmonary tuberculosis, submitted to bilateral thoracoplasty (*See Case Report W S*)

(*a*)



(*b*)



(c)

Fig 154 (*cont*)



(d)



(e)

that it is wise, when the apical mobilization has been completed, to close the hole in the pleura and aspirate the air from the pleural space immediately Failure to do so, increases the physiological upset of the operation and also the amount of pleural effusion which occurs

Case Report W S

Female aged 29 years

4 9 41 Admitted to hospital for thoracoplasty with history of pulmonary tuberculosis since March 1939 when patient had cavity in left apex, 2 5 39 left phrenic crush with apparent relief of symptoms

Fig 154*a* Condition on admission cavity at right apex and small one at left apex general condition fair, sputum positive, it was decided to do a right thoracoplasty first

19 9 41 – 16 10 41 Three-stage right thoracoplasty with apical mobilization (Fig 154*b*)

26 5 42 Discharged to sanatorium with slight pyrexia and positive sputum, after course of sanatorium treatment, patient remained fit and well until April 1947 when sputum again became positive after a cold

Fig 154*c* Condition at this time cavity in left apex, confirmed by tomograph (Fig 154*d*)

13 10 47 Admitted to hospital for left thoracoplasty

11 11 47 – 26 11 47 Two-stage left thoracoplasty, ribs 1–4 with mobilization of the apex Patient developed left pleural effusion which cleared up fairly quickly Convalescence was complicated by abdominal pain and discomfort with intermittent diarrhoea Radiological examination of gastro-intestinal and renal tracts were negative, this slowly cleared up

18 2 49 Patient feeling well doing her housework, cough and trace of sputum which was negative on culture

Fig 154*e* Condition after bilateral thoracoplasty

Damage to the sympathetic — Many patients develop a Horner's syndrome llowing the operation This may be temporary and is due to mild trauma

only, but it may be permanent, and in these cases, is due to division of the sympathetic, which is often deliberate in cases where the apex is very adherent It is but a small price to pay for a successful cavity closure.

Damage to the thoracic duct—This again is often unavoidable in adherent cases If recognized and dealt with, it leads to no disability In a number of cases in which the thoracic duct has been ligated, no alteration in nutrition has been observed, in fact all cases have put on weight, probably as a result of the efficient control of their tuberculosis

Opening of the cavity.—This is, of course, a serious accident, but if the cavity is closed and the apex mobilized sufficiently, it can be expected with reasonable certainty that nothing untoward will result

Plombage with plastic materials

Many modifications of the operation of thoracoplasty have been devised, the most valuable being that described by Cleland (1950)

The principle underlying this operation is the mobilization of the apex of the lung, with as little disturbance of the bony thoracic cage as possible, and the maintenance of the apex in its relaxed position by means of leucite balls placed in the residual space

Small portions of the second and third ribs are removed to allow of mobilization of the apex which is liberated sufficiently to relax the diseased area completely; the space left within the bony cage is then filled with leucite balls which are left *in situ* permanently, unless some indication for their removal arises

The operation, when performed by Cleland, gives good results, although closure of the cavity takes a longer time to achieve in the average case than with the standard extra-fascial operation

The advantages of the operation are that the degree of deformity is less than with the standard operation, paradoxical movement of the lung is avoided, and thus the operation can be performed in one stage. The disadvantage of the operation is the insertion of a foreign body. Although pure leucite seems to be free from objectionable reactions, if infection occurs, removal of the leucite balls becomes imperative, and the closure of the residual space is correspondingly difficult The author has no personal experience of this operation and reports from different centres, apart from that quoted above, are varied

Post-operative complications

The chief complications are those of atelectasis and spread of the disease, both resulting from bronchial aspiration and tuberculous infection of the extra-fascial space.

Atelectasis

The published frequency of post-operative atelectasis depends wholly on the frequency with which radiological examination has been carried out in the series. [illegible] of hours, [illegible] examina- [illegible] s, but it is probable that it occurs in about 80 per cent of cases to a [illegible] ser degree

Clinically these cases can be subdivided into three clinical groups



FIG 155 — Female, aged 39 years Failed thoracoplasty right side with persistent cavity, scattered infiltration left apex, submitted to re-operation with re-mobilization of apex (*See Case Report C R*)

(*a*)



(*b*)



(c)



(d)

The asymptomatic cases —In this group, there are no toxic symptoms, and apart from a careful clinical and radiological examination, the condition would be unsuspected It is worthy of note that breath sounds over the base on the operated side can be absent when there is no atelectasis, this is due to the markedly diminished movements of this side in certain patients, in the latter circumstances there will be resonance and not dullness to percussion over the area

Case Report C R

Female aged 30 years

21 11 45 Admitted to hospital with history of having had thoracoplasty done in June 1944 with failure of cavity closure and sputum conversion General condition fair B S R 12

Fig 155a Condition on admission thoracoplasty right side, scattered infiltration left apex

Fig 155b Tomograph of right apex shows cavity under thoracoplasty

4 12 45 Revision thoracoplasty 1st stage, regenerated portions of ribs 1, 2, 3 and 4 resected, apex was remobilized down to the level of the 5th rib posteriorly

20 12 45 Revision thoracoplasty 2nd stage, regenerated portions of ribs 5, 6 and 7 resected and portion of normal 8th rib, no further mobilization, post-operative course smooth and uneventful

10 12 48 Quite fit and well, no cough or sputum

Fig 155c Condition after re-operation

Fig 155d Tomograph shows no evidence of cavitation

The toxic cases —These patients include two groups and present toxic signs of varying severity, the temperature and pulse and often respiration are raised There is usually increase of cough and sputum, loss of appetite and a certain apathy which is absent in the first group

These patients can be further subdivided, usually by the outcome of the case Those in which the atelectasis clears up and those in which there is progressive deterioration of varying rapidity sometimes leading to a fatal termination

Pathology —The underlying pathology of these two is different The asymptomatic group are suffering from a simple atelectasis caused by a plug of sputum in the lobar bronchus, which is generally coughed up In the toxic group, the atelectasis is infected In those cases which come to post-mortem examination the condition is indistinguishable from that of a septic inhalation bronchopneumonia which is usually the cause of death In some of the non-fatal cases, lung necrosis may occur with the formation of a lung abscess Two such cases have been cured by external drainage and completion of the thoracoplasty Although there is no evidence in such cases of a tuberculous lesion, it is generally possible, in non-fatal cases, to demonstrate, 2 or 3 years later, scattered calcifications throughout the lobe It seems probable, therefore, in these infected cases, that at the onset of the lesion, the non-tuberculous element is predominant, but there is little reason to doubt that eventually a tuberculous process will manifest itself The incidence of the fatally infected cases is fortunately rare, not more than about 3 per cent, but the non-fatal cases are more frequent In view of the probability of tuberculosis developing in these cases, it is sound practice to carry the thoracoplasty to the base in all cases of atelectasis which persist for a period of 3 weeks Failure to follow this practice in some cases has lead to late excavation in the uncollapsed area

Tuberculous infection of the extrafascial space

This complication has, without doubt, increased with the extended use of apical mobilization in the more advanced cases.

Most commonly the infection manifests itself any time between 6 and 12 weeks following the operation, although it may occur earlier. Its cause is not always easily determined, quite obviously it must come from either the lung or the lymphatics or lymph glands. The latter is probably the most common source Pathological examination of glands removed at operation show that a high percentage are the seat of a tuberculous infection, and, interestingly enough, not an insignificant number show typical sarcoid changes In one personal case, a quiet necrosis of the cavity wall occurred following operation, leading to infection of the space , the cavity was sewn up and closed, but the infection of the space persisted

Before the advent of streptomycin, this complication was almost untreatable, but the results obtained with the use of this drug have been most encouraging. If the condition can be recognized early and treatment with streptomycin commenced promptly, the majority of these cases will heal spontaneously.

Pyogenic infection of the space does occur, but its control, once recognized, is relatively simple.

Post-operative care

Post-operative management of the case is directed mainly to the minimizing of the incidence of atelectasis and the prevention of scoliotic and postural deformity

Atelectasis is minimized by encouraging the patient to raise his secretions This entails close supervision, assistance by the nurse with manual support of the operated area to assist coughing, posturing of the patient on the sound side 2 or 3 times daily while coughing to enable him to empty the operated side, and the exhibition of expectorants, such as saline expectorants and ammonium carbonate, if the sputum is viscid and tenacious. Coughing in the early pre-operative days is painful, and morphine should not be withheld , to do so is not only unkind but harmful as the patient will suppress his cough rather than face the pain. Morphine, ¼ grain, should be given 4-hourly if necessary, larger doses will tend to dull the cough reflex

The paradoxical movement of the operated side can be decreased by strapping the chest and the fixation of suitable pads over the mobile areas.

For ... trained physio- ... t
therap[illegible]
knows

The exercises are directed to maintaining the correct position of the head and spinal column and the movements of the arms at shoulder joints and scapulae After the second stage, when the scapula is embedded in front of the eighth [illegible]

for the relief of pain.

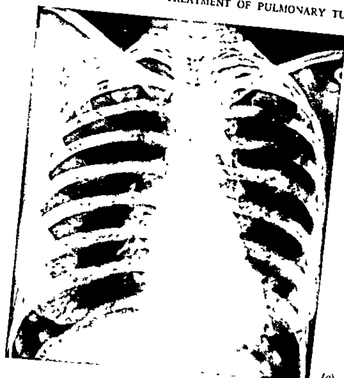
Results of thoracoplasty

Total number of cases (treated in two institutions)		518	
Early mortality (patients unable to leave hospital)		55	(10 6%)
Number of cases followed up		421	
Cavity closure and sputum negative or no sputum		338	(80 3%)
Cavity unclosed or sputum positive		41	(9 7%)
Late mortality before 1 year	8		
after 1 year	34	42	(10%)
Cases insufficiently followed up		6	
Cases operated on less than 1 year ago		36	

CAVITY DRAINAGE

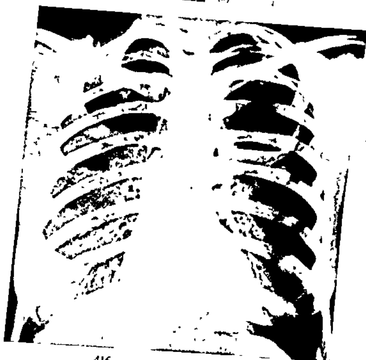
The beneficial effects from cavity drainage stem from two chief underlying factors Elimination of the inflationary element in the cavity which is dependent on the expiratory stenosis, leads to first an improvement in the blood supply to the cavity walls, and in consequence, if the patient's resistance against his disease is good, the initiation of healing of the tuberculous process, and secondly, to a decrease in the size of the cavity, because the inherent retractility of the pulmonary tissue is not now impeded by the tension within the cavity Often secondary advantages also accrue, the secretions from the cavity wall now discharge *via* the drainage hole, and in consequence, cough and the production of sputum is decreased Cavity drainage itself, however, does not alter the condition of the draining bronchi Disease in the latter situation needs specific treatment directed to the bronchi themselves, either to induce their closure, or possibly to the re-establishing of free open drainage Closure can be brought about either by superadding a relaxation procedure, such as thoracoplasty, or by further increasing the stenotic tendency by the application of chemical escharotics There is some evidence at present to suggest that the combination of topical and parenteral streptomycin with cavity drainage may so re-establish free bronchial drainage that the cavity may close

Cavity drainage is carried out after the method introduced by Monaldi or some modification of it A tube is inserted through the chest wall and lung into the cavity, after having previously determined that the visceral and parietal pleurae are adherent over the site of drainage The latter is most important, as any attempt to drain the cavity across a free pleura will inevitably lead to an empyema In the Monaldi technique, a small bored catheter is introduced through a special cannula The catheter is then attached to a suction pump, suction at a negative pressure of 4 6 centimetres of water is carried out from 8 to 10 hours a day The disadvantage of this form of treatment is, as indicated above, that the bronchial openings are not accessible to treatment The advantages are that many cases, with large cavities and a great deal of surrounding infiltration, can be made fit for thoracoplasty The majority of cases so treated improve in their general condition and their resistance against their disease improves Doubtless the period of time under strict observation and hospital or sanatorium conditions which follows the drainage procedure play a considerable part in producing this improvement. It cannot be gainsaid, however,



(a)

FIG 156 — Female, aged 25 years Giant cavity left apex General condition poor, with constant pyrexia Artificial pneumothorax attempted; abandoned immediately Monaldi drainage decided upon and carried out for five months Thoracoplasty carried out with closure of cavity (*See Case Report E.N*)



(b)



(c)



(d)

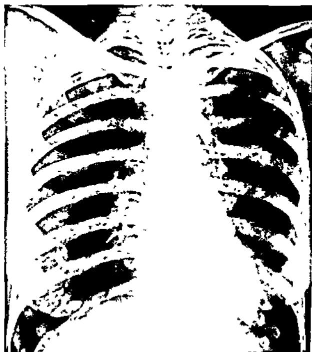
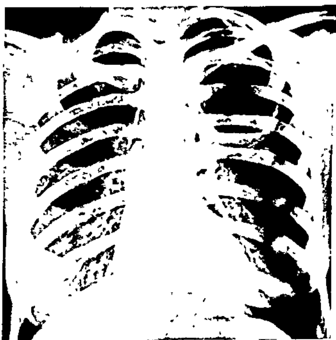


FIG. 156 — Female, aged 25 years Giant cavity left apex General condition poor, with constant pyrexia Artificial pneumothorax attempted, abandoned immediately. Monaldi drainage decided upon and carried out for five months Thoracoplasty carried out with closure of cavity (*See Case Report E.N*)

(*a*)



(*b*)



(c)



(d)

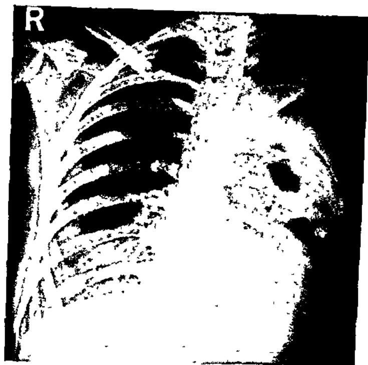


FIG. 156 (*cont.*)

(*e*)



(*f*)

that many cases which are quite unfitted for thoracoplasty can be rendered so by preliminary drainage It is the general experience that thoracoplasty is essential after Monaldi drainage, and in the author's experience, the extent of the thoracoplasty is not materially changed by the fact of preliminary drainage, it is equally true also that the size of the cavity alone does not necessitate preliminary drainage as they can be closed by thoracoplasty alone (Fig 156)

Case Report E N
Female aged 25 years
21 1 45 Admitted hospital with history of cough but no sputum, since August 1944
December 1944, consulted her doctor, diagnosis of pulmonary tuberculosis was made
Skiagram showed cavity in left upper zone
Fig 156a Condition on admission large apical cavity with some surrounding infiltrat-
bronchoscopy showed no evidence of tuberculous bronchitis, general condition poor, 1
to 100, left artificial pneumothorax induced, contraselective
Fig 156b Condition after artificial pneumothorax, artificial pneumothorax aband
Monaldi drainage decided upon
19 6 45 Catheter inserted into cavity
Fig 156c Monaldi tube coiled in cavity, aspirations carried out for five months
Fig 156d Cavity after injection of Lipiodol, note marked decrease in size of cavity
presence of bronchial communication
27 11 45 1st stage left thoracoplasty ribs 1, 2 and 3 and posterior ends of 4 an
removed, mobilization down to aortic arch
Fig 156e Condition after 1st stage
15 1 46 2nd stage thoracoplasty remainder of ribs 4 and 5 and ribs 6 and 7 remove
with remobilization of lung down to level of 7th rib
10 1 49 General condition excellent, working normally, no cough or sputum
Fig 156f Condition following thoracoplasty

Cavity drainage is also carried out as a more major procedure This entails the resection of the appropriate rib or ribs overlying the cavity and then the overlying pleura and the outer wall of the cavity, as is practised in the drainage of an acute lung abscess, obviously it is essential that either a pleural symphysis is present or that one is artificially produced before drainage is undertaken The remaining cavity is packed lightly with Vaselined gauze and at a later date, the bronchial openings which lie on the surface are cauterized with silver nitrate The advantage of this procedure lies in the ease with which the bronchi can be treated

Drainage is preferably used for solitary cavities which are so placed as to make them either unsuitable for major relaxation procedures in that a successful result from such a procedure can be anticipated in only a small percentage of cases, or that the relaxation procedure would entail the collapse of a large area of normal lung in order to cover the cavitated area The former group comprises the cavities which lie anteriorly, those in the pectoral segments of the upper lobe and those lying in the middle lobe The latter group consists of the solitary cavities in the apical part of the lower lobe When these cavities coexist with cavities in the upper lobe then closure can confidently be anticipated, if the mobilization of the lung is sufficiently extensive

LUNG RESECTION

Resection is the most recent of the surgical interventions used for pulmonary tuberculosis This method was obviously prompted, first by the satisfactory results obtained with it in the treatment of suppurative and neoplastic diseases

of the lung, and secondly by the unsatisfactory results obtaine procedures with certain cavities, notably those in the basal segme lobes. At present, 3 groups of tuberculous lesions are submitte (1) closed tuberculous lesions, (2) Bronchostenotic lesions, and (3) ca lesions

Closed lesions

The closed lesions comprise (a) the so-called tuberculomas, (b) stenotic lesions behind which there is a tuberculous bronchiectas strictly limited, and may be present without any evidence of tubercu remainder of the lung, (c) lastly a group of cases which for want o idea of their pathology must be considered as persistent primary foci lymphadenopathy accompanying them tends to confirm this view T feature about these lesions is that the bronchus at the level of surgic is practically invariably healthy, in that there is no evidence of mucosa mucosal involvement by the disease process This is in direct contra cavitated lesions and the stenotic lesions affecting the larger bronchi w mucosa or submucosa is invariably involved.

Bronchostenosis

Bronchostenosis affecting the upper lobe when there is coexisting cavi does not necessarily indicate resection, these cases can be treated satisfa by thoracoplasty Alexander (1937) pointed out that in the great majority of cases, the disease is controlled and the bronchostenosis does not give rise to trouble, personal experience amply confirming this

Bronchostenosis with superadded secondary infection of the bronchial behind the stenosis constitutes a prime indication for resection. Second infection occurs most commonly when the stenosis affects the lower lobe, it is the infection itself which constitutes the main indication for resection, tuberculous element being of secondary importance as an immediate indicatio but it is of considerable importance prognostically in the immediate and lon term view

Bronchostenosis, when it is associated with cavitation of the lower lobe constitutes an absolute indication for resection The risks of superadded infection in the bronchi of the lower lobe and the difficulty experienced in closing cavities situated in the basal segments, make the majority of these cases unsuitable for relaxation methods

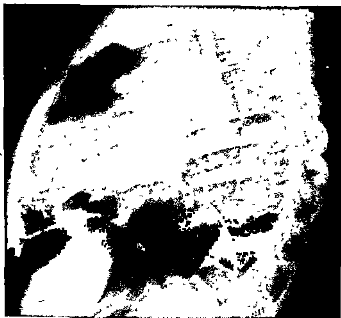
Cavitated lesions

There is at present a tendency to submit certain cavitated lesions to radical extirpation irrespective of their anatomical site, for example large apical cavities if they show any evidence of distension The advocates of resection in this group maintain that distension cavities cannot be closed by thoracoplasty, this is manifestly untrue in the author's experience, these cases react to thoracoplasty in as satisfactory a manner as do other cases, if apical mobilization is carried out sufficiently extensively as to include not only the area of the cavity, but also that of the draining bronchi If the cavity is situated in the upper lobe

Fig 157 — Female, aged 20 years Lesion left lung, pulmonary tuberculosis diagnosed six months later Cavity apex of left lower lobe (*See Case Report I K*)



(*a*)



(*b*)



Fig 157 (*cont*)

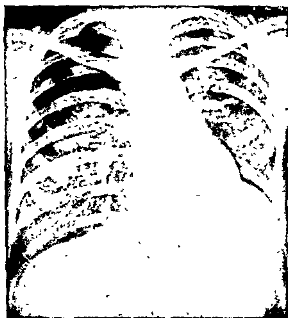
(*c*)



(*d*)



(e)



(f)

extensive methods are either contra-indicated or ineffective, then thoracoplasty is the operation of choice

Resection, however, is not only indicated but *fully justified, in cases with* cavities situated in the basal segments of the lower lobe when there is no disease in the upper lobe (Fig 157)

Case Report I K

Female aged 20 years.

[illegible]

[illegible] the apical part [illegible]

December 1946 · Left phrenic re-crush

July 1947 Cavity appeared in right upper lobe and artificial pneumothorax induced; no adhesions

August 1947 Left phrenic re-crush

[illegible]

Fig. 157*a* Right artificia[illegible] with raised left diaphragm [illegible] shadow

Fig 157*b* Cavity in apical part of lower lobe

Fig. 157*c* and Fig 157*d* Cavity in lower lobe, tomographs of right side failed to show any cavitation, left lower lobectomy decided upon

23 11 48 Left lower lobectomy under streptomycin cover. Later that evening, bleeding in the pleural cavity and wound had to be re-opened; no definite bleeding point but general oozing discovered, this was controlled by fibrin foam

Fig 157*e* (post-operative) Apparent spread in left upper lobe and right lung No severe constitutional disturbances accompanied this

Fig 157*f* 3 months following operation shows practically complete clearing of left-sided *spread and very marked improvement of spread on right side, sputum trace still positive*

Indications

Before resection is contemplated for cavitation in the lower lobe, less drastic forms of treatment should have been tried, that is artificial pneumothorax, *diaphragmatic paralysis and pneumoperitoneum About 30 per cent of cavities* will close after these minor interventions, which should be persisted with for about 3 to 4 months, before a decision is made as to the necessity for radical measures

A combination of cavitation in the basal segments of the lower lobe and cavitation in the upper lobe sometimes may indicate that primary resection will *be preferable to thoracoplasty It, however, should be pointed out that resection* can be undertaken if thoracoplasty fails, and it is probably safer to undertake a thoracoplasty in the first place, the degree of destruction of the lung influencing the decision considerably

The condition of the contralateral lung will seriously influence the decision Cavitation in it, will, as a general rule contra-*indicate resection, but if the cavity* has been closed either by an artificial pneumothorax or some other lesser measure, resection need not necessarily be ruled out, providing that the extent of the resection is sufficiently limited. The presence of limited non-cavitated parenchymal disease, if it is quiescent, does not necessarily contra-indicate resection

Tomographs should be taken of both lungs, using at least 1 centimetre cuts,

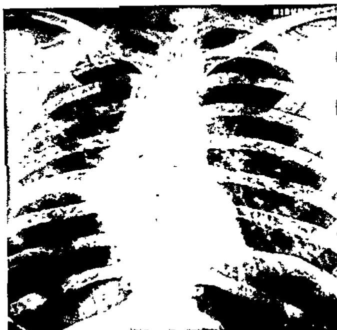


FIG 158 — Male, aged 32 years Eight years history of pulmonary tuberculosis with bilateral disease Admitted to hospital with cavities in right upper lobe and also in right lower lobe Right pneumonectomy performed with lateral thoracoplasty (*See Case Report H W*)

(*a*)



(*b*)

in order to exclude the presence of cavitation. It is worthy of note that it is always possible to palpate lesions in the lung, on thoracotomy, which have not been demonstrated, or *at least recognized, in the pre-operative* radiographs, in consequence, pre-operative investigation cannot be too careful.

Bronchoscopy should likewise be undertaken before resection is undertaken Gross tracheo-bronchitis or stenosis is easily recognized; not infrequently, however, the bronchial mucosa has been reported as normal when histological examination of the removed specimen has proved it to be practically completely replaced by tuberculous granulation tissue. A biopsy of the mucosa should be taken when the bronchoscopy is undertaken

Case Report H W.

Male aged 32 years

July 1948 Admitted to hospital with history of pulmonary tuberculosis since 1940 This was followed by two or three periods of sanatorium treatment with return to work at intervals June 1944 Patient became worse and the disease was found to be bilateral with cavitation in both upper lobes Again treated by

cavities apparently closed May 1946

h detachment

ce of sputum

Technique

The operation is undertaken with a cover of streptomycin, ½ gramme of which is given intramuscularly twice daily for 3–4 days before operation and is continued for about 3 weeks after the operation

When a lobectomy has been performed, it is probably wiser permanently to interrupt the phrenic nerve *Pneumonectomy should be followed by a lateral* thoracoplasty Both of these procedures have the advantage that they prevent subsequent over-distension of the remaining lung tissue and the subjecting of unidentified foci to undue strain.

Many cases have had a pneumoperitoneum induced before operation as a therapeutic measure and this should be maintained; if this has not already been carried out one should be induced. The value of the pneumoperitoneum, apart from its *value in the control of toxaemia, lies in the reduction of the volume of the* hemithorax After lobectomy, this facilitates the filling of the hemithorax by the remaining lobe After pneumonectomy, a smaller thoracoplasty is necessary because of the elevation of the diaphragm

It is impossible to give an accurate assessment of the long-term value of lung resection until a sufficient number of cases have been followed up for 5–10 years. The immediate results of cases followed up to 3 years, is, on the whole, encouraging, *and it is not unreasonable to suppose* that resection will continue to play an increasing part in the control of the disease

esults of lung resection		
Total resections	76	
Cavitated lesions	48	(Early deaths 5 late deaths 1)
Closed tuberculous lesions	18	(No deaths)
Stenotic lesions	10	(Early deaths 1)
Pneumonectomy	38	(Early deaths 5 · late deaths 0)
Lobectomy	38	(Early deaths 1 late deaths 1)

BIBLIOGRAPHY

General

Beven, G (1952) "The Effects of Pregnancy on Pulmonary Tuberculosis" *Tubercle*, 33, 13

Cohen, R C (1946) "Pulmonary Tuberculosis and Pregnancy" *Brit J Tuberc*, 40, 10

Geddes, J E (1952) "Rehabilitation and Resettlement" *Tubercle*, 33, 2

Heaf, F R G (1948) "Accommodation for the Tuberculous" *Tubercle*, 29, 2

Pugh, D L, Jones, E R, and Martin, W J (1951) "Domiciliary Treatment of Pulmonary Tuberculosis with Combined Chemotherapy" *Tubercle*, 32, 256

Artificial Pneumothorax

Amberson, J B, Jun (1930) "The Indications for and the Results of Artificial Pneumothorax in Pulmonary Tuberculosis" *Ann intern Med*, 4, 343

Bentley, F J (1936) "Artificial Pneumothorax experience of London County Council" *Med Res Coun Spec Rep Ser*, 215

Bloch, R G, Tucker, W B, and Adams, W E (1941) "Standards and Criteria in Artificial Pneumothorax Therapy" *J thorac Surg*, 10, 310

Burrell, L S T (1933) "Late Results of Treatment by Artificial Pneumothorax" *Lancet*, 2, 1414

Forlanini, C (1882) "Contribuzione della terapia chirurgica della tisi Ablazione del pulmone? Pneumotorace artificale?" *Gazz Osp Clin*, 3, 537

Jennings, F L, Mahill, P M, and Nemie, F C (1940) "Artificial Pneumothorax resumé of 20 years experience" *Amer Rev Tuberc*, 42, 431

Macfie, J O, and Alexander, A J P (1932) "Artificial Pneumothorax Two hundred cases" *Lancet*, 1, 450

Maher-Loughnan, G P (1950) "An Investigation into the Factors Contributing to Relapse in Cases Treated by Unilateral Artificial Pneumothorax" *Tubercle*, 31, 74

Mariss, W H (1942) "Pneumothorax Treatment The subsequent history of tuberculous patients after their selection for pneumothorax" *Amer Rev Tuberc*, 46, 628

Mitchell, R S (1951) "Artificial Pneumothorax a statistical analysis of 557 cases initiated in 1930–39 and followed in 1949" *Amer Rev Tuberc* 64, 1

Morland, A (1949) "Pleural Shock" *Lancet*, 2, 1021

Rist, E, (1927) "Results of Artificial Pneumothorax in Pulmonary Tuberculosis" *Amer Rev Tuberc*, 15, 294

Scadding, F H, Nicholson, H, and Hoyle J C (1951) "Artificial Pneumothorax" *Quart J Med*, 20, 313

Shaw, C (1933) "The Value of Artificial Pneumothorax in Pulmonary Tuberculosis" *Quart J Med*, 2, 179

Simmonds, F A H, and Martin, W J (1948) "Results of Sanatorium Treatment and Collapse Therapy" *Amer Rev Tuberc* 58, 537

Sinding Larsen, C M F (1937) "On Collapse Treatment of Pulmonary Tuberculosis Clinical adaptation and follow up examination of material from Vejlefjord Sanatorium, 1906–32" *Acta med Scand*, Suppl 80

Trail, R R (1934) "Artificial Pneumothorax, an after history of 113 cases" *Brit med J*, 1, 373

— and Stockman, G D (1932) "After History of Artificial Pneumothorax, comment on 91 successful and 31 unsuccessful cases" *Quart J Med*, 1, 415

Young, F H, and Heaf, F R G (1949) " Discussion on the Place of Artificial Pneumothorax in the Treatment of Pulmonary Tuberculosis." *Proc. R Soc. Med*, 42, 244

Adhesion Section

Anderson, R S, and Alexander, J (1937) " Closed and Open Intrapleural Pneumolysis. Results in 111 and 29 cases respectively " *J thorac Surg*, 6, 502

Chandler, F G (1932) " Adhesion Cutting with Special Reference to the Uses and Limitations of Diathermy and the Use of Separate or Combined Endoscope and Operating Instrument " *Tubercle*, 14, 49

Edwards, P W, Penman, A C, and Logan, J (1944) " Late Results of Closed Intrapleural Pneumolysis " *Brit med J*, 2, 270

Jones, H A (1945) " Indications for Intrapleural Pneumolysis : A review of 567 thorascopic examinations " *Amer Rev Tuberc*, 52, 355

Marcus, H, and Pinner, M (1946) " Results of Pneumolysis." *Amer Rev. Tuberc.*, 54, 25

Moore, J A (1934) " Intraplueral Pneumolysis A critical review." *J. thorac Surg*, 3, 276.

Smart, J (1939) " Thoracoscopy and Adhesion Section with Special Reference to Indications and Results " *Tubercle*, 21, 81

Diaphragmatic Paralysis

Anderson, B W (1934) " Evulsion of the Phrenic Nerve in the Treatment of Pulmonary Tuberculosis " *Quart J Med*, 3, 15

Aufses, A H (1937) " Phrenic Nerve Operations in the Treatment of Pulmonary Tuberculosis " A review. *Medicine*, 16, 139

Edwards, P W, and Stevens, J S T (1938) " Phrenicectomy in the Treatment of Pulmonary Tuberculosis " *Tubercle*, 19, 252.

Potter, B P, Berry, F. B, and Bartine, F (1937) " Phrenic Interruption in the Treatment of Pulmonary Tuberculosis A five year survey and follow up " *J thorac. Surg*, 6, 424

Thorburn, G, and Riggins, H M (1941) " Temporary Phrenic Paralysis in Selected Cases of Partially Effective Pneumothorax. A report on 100 cases " *Trans. Nat. Tuberc. Assoc*

Pneumoperitoneum

Banyai, A L (1934) " Therapeutic Pneumoperitoneum " *Amer. Rev Tuberc*, 29, 603

— (1946) " Pneumoperitoneum in the Treatment of Pulmonary Tuberculosis " *Tuberculology*, 8, 3

Nord Med, 45, 127

" Pneumoperitoneum in the Treatment of

, 39, 528.

eritoneum in the Treatment of Pulmonary

cle, 32, 26

Extrapleural Pneumothorax

(1946) " Early and Late Results of Extrapleural Pneumothorax "

ercle, 32, 186.

rac. Surg, 7, 575

t. J Tuberc, 32, 173

leural Pneumothorax: critical survey."

nance of Extrapleural Pneumothorax "

Murstead, E (1951) "Extrapleural pneumothorax in the treatment of pulmonary tuberculosis" *Lancet*, 1, 299
Pannier, R (1949) "Extrapleural Pneumothorax" *Acta tuberc Belg*, 42, 8
Reed, H (1946) "Report on 140 Cases of Extrapleural Pneumothorax in Treatment of Pulmonary Tuberculosis" *Thorax*, 1, 211
Roberts, A T M (1948) "Extrapleural Pneumothorax A review of 128 cases" *Thorax*, 3, 166
Sellors, T H (1938) "Extrapleural Pneumothorax" *Brit J Tuberc*, 32, 182

Thoracoplasty
Bonniot, A, Douady, D, Cohen, R, and Bosquet, P (1951) "Résultats éloignes de 225 thoracoplasties d'indication pulmonaires faites au sanatorium des étudiants de Saint-Hilaire-au-Touvet de 1933–1948" *Rev Tuberc Paris*, 15, 505
Carlsen, H A, Burns, H A, and Wagensteen, O H (1939) "Late Results of Thoracoplasty" *Minn med*, 22, 294
Crimm, R D (1945) "Thoracoplasty Report on 240 consecutive patients" *Amer Rev Tuberc*, 51, 505
de Winter, L (1950) "Report on 1 137 Cases of Pulmonary Tuberculosis Treated by Thoracoplasty in Bruges since 1926" *Acta tuberc Belg*, 41, 165
Dolley, F S, Jones J C, and Paxton, J R (1939) "Late Results of Thoracoplasty An evaluation of results from 114 American clinics in 1,636 cases" *Amer Rev Tuberc*, 39, 145
Freedlander, S O, and Wolpaw, S E (1937) "A Control Group for Studying the End-results of Thoracoplasty" *J Thorac Surg*, 6, 477
Gjessing, M (1948) "Sein resultater etter torakoplastikk" *Nord Med*, 37, 226
Harrison, A W, and Berry F B (1943) "Analysis of 150 Cases of Thoracoplasty for Tuberculosis at Bellevue Hospital" *J Thorac Surg*, 12, 292
Hurford, J V (1941) "Thoracoplasty for Pulmonary Tuberculosis" *Lancet*, 1, 693
Krynski, B (1947) "Survey of Thoracoplasties at Sea View Hospital over a 5-year Period (1937–1942)" *Quart Bull Seaview Hosp*, 9, 144
O Brien, E J, Day, J C, Chapman, P T, and Tuttle W M (1940) "Study of Immediate and Late Results in 511 Patients Subjected to Thoracoplasty" *J Thorac Surg*, 9, 364
Peters, L, and Cornish, P G (1938) "End Results of Thoracoplasty" *Amer Rev Tuberc*, 38, 586
Sellors, T H (1947) "The Results of Thoracoplasty in Pulmonary Tuberculosis" *Thorax*, 2, 216
Semb, C (1935) "Thoracoplasty with Extrafascial Apicolysis" *Acta chir Scand*, 76, Supp 37
Symposium (1942) "Results of Thoracoplasty" *Amer Rev Tuberc*, 45, 349
Tattersall, W H, (1947) "Survival of Sputum Positive Consumptives study of 1,192 cases in county borough between 1914 and 1940" *Tubercle*, 28, 85
Thomas, C P (1942) "Pulmonary Cavities their persistence and closure" *Brit J Tuberc*, 36, 4
— and Cleland, W P (1942) "Extrafascial Apicolysis and Thoracoplasty" *Brit J Tuberc*, 36, 109

Plombage
Cleland W P, and Lucas, B G B (1950) "Thoracoplasty with Plombage A review of the early results in 125 cases" *Thorax*, 5, 248
Davies, H M, Temple, L J, and Stathates C (1951) "The Polythene Pack Operation for Pulmonary Tuberculosis" *Thorax*, 6, 209
Gullbring, A (1931) "Some Experiences with Treatment by Oleothorax" *Acta med Scand*, 75, 258
Matson, R W (1932) "Oleothorax" *Amer Rev Tuberc*, 25, 419
Pollock, W C, and Skinner, R B (1933) "Oleothorax Therapy" *J thorac Surg*, 3, 12

Cavity Drainage
Brunn, H, Shipman, S, Goldman, A, and Ackerman, L (1941) "Tuberculous Cavitation and Transpleural Decompression" *J Thorac Surg*, 10, 485

Eloesser, L , Rogers, W. L , and Shipman, S J (1945) "Treatment of Insufflated Cavities" *Amer Rev Tuberc.*, 51, 7

Monaldi, V (1946) "La ripresa del processi tubercolari dopo trattamento con aspirazione endocavitaria" *Arch. tisiol*, 1, 227

— (1939) "Sul meccanismo della delimitazione del processo tubercolare del pulmone (basi teoriche del procedimento di asperozione endocavitaria" *Ann. Inst Carlo Milanine*, 3, 201.

Murphy, J D , and Koantz, E R. (1950) "Cavernostomy for Residual Cavity after Thoracoplasty: Early close of cavernostomy sinuses under streptomycin protection" *J thorac Surg*, 20, 222

Lung Resection

Alexander, J (1937) *The Collapse Therapy of Pulmonary Tuberculosis* Springfield, Ill ; Thomas

Brantigan, O. C., and Rigden, L (1950) "Resections of the Lung in the Treatment of Pulmonary Tuberculosis" *Arch Surg.*, 60, 58

Chamberlain, J M , and Klopstock, R (1950) "Further Experiences with Segmental Resection in Tuberculosis" *J thorac Surg*, 20, 843

Cruickshank, G , and Papamichael, E (1951) "Pneumonectomy and Immediate Thoracoplasty in the Treatment of Pulmonary Tuberculosis." *Thorax*, 6, 369.

Churchill, E D , and Klopstock, R. (1943) "Lobectomy for Pulmonary Tuberculosis" *Ann Surg*, 117, 641

Day, J C , Tuttle, W M , O'Brien, E J , Hampton, F., and Jackson, T L (1950) "Resection in the Treatment of Pulmonary Tuberculosis" *J. thorac. Surg*, 20, 854

James, R M (1945) "Total and Partial Pneumonectomy in the Treatment of Pulmonary Tuberculosis" *J thorac Surg*, 14, 3

Jones, J C , and Robinson, J L (1950) "Pulmonary Resection in Tuberculosis: its hazards, indications and results" *J thorac Surg.*, 20, 882.

Marer, H C , and Klopstock, R (1945) "Lobectomy for Pulmonary Tuberculosis." *J thorac Surg*, 14, 20

Monod, O , Babon, G , and Low, J (1951) "The Surgical Treatment of Bronchial Fistulas after Lung Resection for Pulmonary Tuberculosis" *Thorax*, 6, 397.

Moyes, E N (1951) "Tuberculoma of the Lung" *Thorax*, 6, 238

Munz, C W , and Adelman, A (1950) "Pulmonary Resection for Tuberculosis with Streptomycin" *J thorac Surg*, 20, 892

Overholt, R H , and Wilson, N. J (1945) "Pulmonary Resection in the Treatment of Tuberculosis A preliminary report" *J thorac Surg*, 14, 55.

Ross, C A (1951) "Pulmonary Resection for Tuberculosis in Children" *Thorax*, 6, 397

Sarot, I A (1949) "Extrapleural Pneumonectomy and Pleurectomy in Pulmonary Tuberculosis" *Thorax*, 4, 173

Sellors, T H , and Hickey, M D (1949) "Excision of the Lung for Pulmonary Tuberculosis" *Thorax*, 4, 82

Waddington, J K B (1951) "Thoracoplasty Concomitant with Resection for Pulmonary Tuberculosis" *Thorax*, 6, 230

CHAPTER 17

THE CHEMOTHERAPY OF PULMONARY TUBERCULOSIS

JOHN CROFTON

THE CHEMOTHERAPY of tuberculosis is in a state of rapid evolution. Many substances have been reported to be bacteriostatic to tubercle bacilli *in vitro* but only a very small proportion have an effect on experimental tuberculosis in animals, and most of these have proved too toxic for use in man The following drugs are the only ones in current clinical use in pulmonary tuberculosis.

1 Streptomycin
2 Dihydrostreptomycin
3. *Para*-aminosalicylic acid (P A S) and its salts
4 The sulphones
5 The thiosemicarbazones
6 Analogues of nicotinamide

Gold salts were advocated for many years but were toxic and probably ineffective, their use has now been generally abandoned

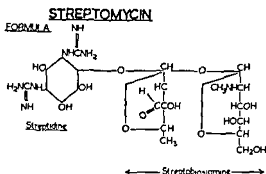
STREPTOMYCIN

History

In an attempt to find an antibiotic which would be effective against bacteria not susceptible to penicillin, Waksman in the United States carried out a systematic investigation of soil fungi In 1944 with his colleagues (Schatz, Bugie and Waksman, 1944), he described streptomycin, a substance derived from a soil fungus *Streptomyces griseus*, and found that *in vitro* it was effective against a considerable range of bacteria including *Mycobacterium tuberculosis* In the same year Feldman and Hinshaw at the Mayo Clinic tested the new antibiotic in experimental tuberculosis in guinea-pigs and found its effect was far greater than that of any previous drug (Feldman and Hinshaw, 1944 ; Feldman, Hinshaw and Mann, 1945) As the toxicity for animals was also slight they then used it in man with suggestive results (Hinshaw and Feldman, 1945). Among the large number of reports which followed the most conclusive was the carefully controlled trial of streptomycin in acute bronchopneumonic tuberculosis by the Medical Research Council of Great Britain (Medical Research Council, 1948a) Early in these trials it was found that, in a high proportion of cases of pulmonary tuberculosis, bacilli isolated after treatment were resistant to streptomycin The most important recent advance has been the discovery (Medical Research Council, 1950 , Tucker, 1949) that the incidence of resistant tubercle bacilli can be very reduced by giving sodium *p*-aminosalicylate at the same time as the streptomycin.

Pharmacology

Streptomycin is an organic base with the following structural formula:



Streptomycin is usually supplied either as the hydrochloride, or as the sulphate or as the calcium chloride double salt A mixture of the last two salts in the test tube results in a precipitate of calcium sulphate so it is best in an individual patient to avoid changeover from one to the other unless there has been an interval of several weeks. Streptomycin is readily soluble in water. It is stable at room temperature in powder form in the ordinary commercial sealed ampoules for at least a year; even in solution there is no loss of potency for 2 months or more at a temperature of 38° C. or below The optimal *p*H for bacteriostatic action is about 7 7, for tubercle bacilli the drug is about four times less effective at *p*H 6 6

Dosage

In pulmonary tuberculosis the usual dose is at present 1 gramme a day intramuscularly This has been found to combine maximal effectiveness with minimal toxicity. It is commonly given in a single daily dose

There is some indication that 1 or 2 grammes of streptomycin every third day, combined with 12 grammes of P.A S. daily, may be as effective clinically as 1 gramme of streptomycin given daily without P.A S In a trial on a limited number of cases no streptomycin-resistant tubercle bacilli were isolated after 120 days on the combined treatment (Tempel and his associates, 1950). If these findings are confirmed such a régime may prove to be the treatment of choice, at any rate in the less severe forms of pulmonary tuberculosis But at the time of writing not enough is known to recommend this method for general use.

Doses of 2 grammes a day may be given in severe cases of miliary tuberculosis in adults For children the daily dose should be 10–20 milligrams per pound body-weight, with an upper limit of 1 or 2 grammes, depending on the seriousness of the condition From 1 to 3 grammes may be given intrapleurally in 10 millilitres of distilled water. No pleural reactions occur Administration by mouth, by inhalation or intravenously is not recommended in tuberculous conditions. Streptomycin has been given directly into tuberculous cavities (Tanner and his colleagues, 1948), but no clear advantage for this method has been demonstrated

Absorption

An intramuscular dose of 0·5 gramme usually gives a maximum serum level of 15–30 micrograms per millilitre at ½–1 hour after injection, falling to 4–8 micrograms per millilitre at 6 hours A dose of 1 gramme gives a maximum of 20–50 micrograms at ½–1, falling to 4–10 micrograms at 6 hours and less than 1 microgram at 24 hours

Distribution

After intramuscular injection levels in pleural fluid are usually a little lower than average serum levels, the level partly depending on the degree of pleural inflammation Scanty data suggest that concentrations in tuberculous cavities may be up to about half the serum level and in sputum rather higher (Steenken, D'Esopo and Wolinsky, 1947) With intrapleural injection of 1 gramme of streptomycin pleural fluid levels of 10–160 micrograms per millilitre and blood levels of 5–10 micrograms per millilitre have been recorded after 48–72 hours.

Excretion

Streptomycin is mainly excreted unchanged by the kidneys From 60 to 80 per cent of an intramuscular dose is lost in the first 24 hours The rate of excretion then falls off slowly and it is possible that, at any rate after the termination of a course, minute quantities may be excreted for a matter of weeks Excretion is mainly glomerular so that caronamide is ineffective in enhancing blood levels, but high levels may occur if the renal function is poor In such cases there should be frequent estimations of the streptomycin level in the blood serum and the dose must be appropriately scaled down, otherwise severe toxic reactions may occur

Urinary concentrations of over 1,000 micrograms per millilitre, which are not infrequently obtained, may reduce Benedict's or Fehling's solution and mimic glycosuria

Antagonists

Streptomycin is not destroyed by enzyme systems and is not antagonized by pus or by P A S Its action is inhibited by inositol, a substance that can be extracted from heart and brain, by cysteine, which is employed for this purpose in the laboratory, and by some other less important substances

Mode of action

In vitro streptomycin is bacteriostatic to tubercle *bacilli* in a concentration of one microgram per millilitre or less, with some variation according to the [illegible] con- [illegible] time [illegible] arrod, [illegible] is are required in order to kill resting bacilli, in fact very high concentrations may fail to do so (Corper and Cohn, 1949) As yet there is no clear evidence as to how streptomycin damages tubercle bacilli Experiments in animals suggest that it is relatively ineffective in the early stages of infection The bacteriostatic and

bactericidal effects become apparent only after sensitivity to tuberculin can be demonstrated (Steenken and Pratt, 1949; Jensen, 1949) It may be that the immune processes of the animal are necessary for the action of the drug *in vivo*. An alternative explanation is that in the early stages of infection the bacteria are within cells and cannot there be reached by the streptomycin.

Toxicity

When given for short periods streptomycin is relatively non-toxic; but in tuberculosis, when it must be given for weeks or months, toxic manifestations are not uncommon Much the most important is the effect on the vestibular apparatus

Vestibular disturbances

The exact site of action of streptomycin on the vestibular apparatus is uncertain though on the whole the evidence suggests that the primary damage is to the cells of the labyrinth (Tucker, 1949; Bignall, Crofton and Thomas, 1951) The main symptom is giddiness With a dose of 1 gramme a day this is usually encountered between the fourth and ninth week of treatment, with 2 grammes a day between the third and the fifth week. Giddiness occurs mainly on movement and in the early stages even reading may be difficult, probably owing to incoordination in eye movement On a daily dose of 2 grammes of streptomycin more than 50 per cent of cases complain of giddiness but with 1 gramme a day the incidence is substantially less, usually under 30 per cent. Some cases, who make no spontaneous complaint, may show vestibular impairment on objective testing When giddiness is slight it usually lasts for only a few days or weeks, even if streptomycin is continued, but when giddiness is severe, and especially in middle aged or elderly people, symptoms may continue for many months. When there is vestibular disturbance slight nystagmus can often be demonstrated; but impairment of caloric reactions is the most valuable objective test This consists of diminution or absence of the nystagmus which normally occurs when water at 30° or 44° C is run into the external auditory meatus, using the method of Fitzgerald and Hallpike (1942). There may be some variation in response during the course of treatment but when the caloric reactions have been lost over a number of weeks they are likely to remain absent for many months Eventually there may be some degree of recovery. Abnormalities in the vestibular tests may persist long after the patient has ceased to complain In such cases it is thought that the patient compensates for the loss of vestibular function by using his eyes and kinaesthetic senses. On close questioning it will often be found that he is still affected in the dark or on turning suddenly Objectively this is best demonstrated by asking him to walk down a line with his eyes closed, though this test is less reliable than the caloric reactions

If a pregnant woman is treated with streptomycin there is no evidence that the vestibular apparatus of the foetus is affected (Watson and Stow, 1948)

There is slight evidence that the use of antihistamine drugs prophylactically may reduce the incidence of vestibular damage (Bignall, Crofton and Thomas, 1951). But the evidence at present is insufficient to recommend their use, except in those patients on exceptionally large doses of streptomycin, in the elderly or

in those with poor eyesight. In such cases Anthisan 100 milligrams may be given 4 times a day by the mouth, or Phenergan 50 milligrams at night and Anthisan 100 milligrams about 4 p m This treatment must be started at the beginning of the course of streptomycin and continued throughout

Deafness and tinnitus

These are unlikely to be encountered when streptomycin is used intramuscularly in the doses recommended

Skin rashes and fever

Skin rashes may occur (Cohen and Glinsky, 1949 , National Research Council, 1946), usually within the first 3 weeks of treatment but occasionally later Commonly the rash is urticarial or erythematous with little or no increase in fever Such rashes usually disappear within a few days even though streptomycin is continued If itching is troublesome antihistamine drugs are worth giving Sometimes the rash is accompanied by a brisk febrile reaction and may even progress to frank exfoliative dermatitis Fever may also occur in the absence of a rash Both streptomycin and the accompanying P A S should be stopped in such severe cases, as the reaction may be due to either or to both After an interval each drug should be tried again separately When one or more doses have been given there will probably be a reaction to whichever drug is responsible If the reaction is due to streptomycin it is possible in most, if not all, cases to desensitize the patient with small ascending daily doses Usually an initial dose of 0 1 gramme is small enough and the full dose can be reached over 10 days or so, but in some cases it is necessary to start with 50 or 100 micrograms If, in an unusual case, desensitization is unsuccessful, dihydrostreptomycin may be tried

Lymph gland enlargement —Sometimes lymph gland enlargement may accompany the fever, whether or not the rash is present As in other drug reactions the clinical picture may resemble rubella

Nausea and vomiting

Nausea (Bignall, Crofton and Thomas, 1951 , Bignall and Crofton, 1949), and sometimes vomiting, occurs in more than 50 per cent of patients receiving 2 grammes of streptomycin a day, but in less than 20 per cent on 1 gramme With the present dosage of 1 gramme a day and when, as is now usual, P A.S is also being given the nausea is more likely to be due to the P.A S A delayed onset might suggest streptomycin as the cause , in this case the nausea usually starts between the second and the eighth week Nausea due to streptomycin is often slight and transient, but in a few cases is severe and prolonged Such cases respond well to antihistamine drugs, such as Benadryl 50 milligrams or Anthisan 100 milligrams 3 times a day, though these may have to be continued for the remainder of the course

Paraesthesiae round the mouth occur occasionally, often soon after starting treatment, but clear up after a few days or weeks

Blood changes

Eosinophilia is found quite commonly but is unimportant (Tucker, 1949)

Urinary changes

Albuminuria (Tucker, 1949) may occur, especially in children on high dosage. Serious kidney damage is rare, but there may be some risk of added damage in cases whose renal function is already impaired. In such a case the advisability of giving streptomycin must be considered with particular care and the streptomycin dosage controlled by repeated serum estimations.

Vitamin deficiencies

Sore tongue, mouth ulcerations, excoriated lips, and dermatitis of the scrotum have been described in cases on streptomycin (Sumner, 1949), and were attributed to riboflavine and nicotinic acid deficiencies (Beham and Perr, 1948). The deficiency was thought to be due to alteration of the normal intestinal flora. This has not been proved but it is worth while giving supplements of these vitamins to such cases.

Dermatitis in handlers of streptomycin

Dermatitis in those handling streptomycin (Crofton and Foreman, 1948) is not infrequent. Nurses may become sensitized after weeks or months of exposure. The rash is most common on the flexures of the elbows and round the eyes, the hands oddly enough being less often affected. The degree of sensitivity may be remarkable, some patients cannot even enter a ward in which streptomycin is being given without developing symptoms. An intradermal test with 50-100 micrograms of streptomycin in 0.1 millilitre of normal saline solution gives a positive flare, perhaps with a wheal also, usually maximal at 6 hours after injection but sometimes at 12 or 24 hours. The skin test may become positive in the absence of symptoms, such individuals have been sensitized and may develop a rash later. Everyone handling streptomycin should wear rubber gloves. The gloves should be donned before the containers are opened. Both gloves and hands should be thoroughly washed after finishing the injection.

People sensitive to streptomycin can be desensitized. This has to be done with care, under close supervision and preferably under cover of antihistamine drugs. The patient should receive daily intramuscular doses starting with 50 micrograms and working up very slowly, over 4-6 weeks, to 1 gramme.

Streptomycin resistance

One of the major disadvantages of streptomycin has been that bacteria may acquire the capacity to resist its action.

Method of testing

Sensitivity to streptomycin is tested *in vitro* by culturing the tubercle bacillus from the sputum and from the culture adding a standard inoculum to a series of tubes containing media made up with ascending concentrations of streptomycin (Medical Research Council, 1948b). A standard sensitive tubercle bacillus is tested at the same time and the highest concentrations in which the organisms grow are compared. When, for instance, the highest concentration in which the bacillus grows is 64 times the highest in which the standard grows the streptomycin sensitivity of the test organism is said to be 64 times less than that of the standard. This is now often expressed as a " resistance ratio " of 64. In the

United States of America and elsewhere the resistance of a strain of tubercle bacilli is often expressed as the number of micrograms of streptomycin per millilitre of medium which inhibits the growth In liquid Dubos medium growth of normally sensitive tubercle bacilli is usually inhibited by from 0 25–0 5 micrograms of streptomycin per millilitre and on solid media, such as Herrold's egg medium, by 1–4 micrograms per millilitre

Resistance tests with the present technique take about 8 weeks to complete, but briefer methods are being developed (Sievers, 1949 , Holt and Cruickshank, 1949)

Streptomycin resistance in miliary tuberculosis

Streptomycin resistant strains of tubercle bacilli are not often encountered in cases of miliary tuberculosis under treatment, but they have been recorded occasionally (Medical Research Council, 1948c)

Mode of development of streptomycin resistance

If cases of pulmonary tuberculosis are treated with streptomycin alone sooner or later cultures from the sputum are likely to yield drug resistant tubercle bacilli It seems that streptomycin sensitive bacilli regularly throw off very small numbers of resistant mutants, even in the absence of streptomycin In a patient under treatment with streptomycin, the resistant mutants are at an advantage and will eventually predominate (Pyle, 1947 , Mitchison, 1950) When the resistant bacilli form 0 1 to 1 per cent of the population the routine test usually employed will show the culture as resistant (Mitchison, 1950) As detected by this test resistant tubercle bacilli usually emerge before the end of the second month of treatment Highly resistant organisms are particularly likely to emerge in cases with extensive cavitation or grossly confluent shadows on the skiagram and in patients who are very ill before treatment starts (Crofton, 1950) The degree of resistance of the organisms isolated varies from case to case Once resistant tubercle bacilli are found at all the degree of resistance in most cases rapidly attains its maximum and remains about that level, though occasionally there may be temporary reversion. The earlier in treatment resistant organisms are isolated the higher usually is the degree of resistance attained (Crofton, 1950)

Permanence of streptomycin resistance

Once resistant bacilli have been isolated there is seldom reversion to sensitivity, so that formerly one had to reckon that an individual patient was only likely to benefit from a single course of streptomycin Moreover, resistant bacilli could spread to others and give rise to tuberculosis which differed only in being insusceptible to streptomycin Several such cases have been recorded (Furtos and Doane, 1949 ; Brennan and Wichelhausen, 1949)

When a *strain is isolated of resistance ratio more than 64* it is probable that streptomycin will be ineffective in treatment The significance of strains with resistance ratios of from 8 to 32 is less certain It is probable that clinically the drug is less effective against such strains, but nevertheless these patients when treated with streptomycin are more likely to become sputum negative than are patients from whom highly resistant strains are obtained (Crofton, 1950)

Methods of combating streptomycin resistance

Various methods of intermittent dosage have been employed in an attempt to delay or prevent the emergence of streptomycin resistant tubercle bacilli. With the possible exception of a *régime* in which 1 gramme is given every third day (Tucker, 1949), these attempts have been unsuccessful Preliminary results suggest that the giving of sulphone drugs at the same time as streptomycin does reduce the incidence of streptomycin resistant bacilli to an important degree Bernard, Nouvion and their colleagues, 1950) No adequate data are yet available about the use of the thiosemicarbazone drugs for this purpose. The most important method of combating streptomycin resistance is the use of sodium *para*-aminosalicylate. It has now been established (Medical Research Council, 1950), that if this drug is given orally in doses of 5 grammes four times a day at the same time as 1 gramme of streptomycin daily intramuscularly, there is a very great reduction in the proportion of cases from which streptomycin resistant tubercle bacilli are isolated Smaller doses are probably less effective (Tucker, 1949) Cases on the combined treatment also do somewhat better clinically and it is clear that it is no longer justifiable to use streptomycin alone in pulmonary tuberculosis.

DIHYDROSTREPTOMYCIN

Dihydrostreptomycin (Hobson and his colleagues, 1948 , Carr and his associates, 1949) is derived from streptomycin by treating the latter with hydrogen in the presence of a catalyst Dihydrostreptomycin hydrochloride is painful on injection and may give rise to muscle necrosis , the sulphate, which is innocuous in this respect, should therefore be used (Lincoln and his colleagues, 1950) Dihydrostreptomycin is less toxic than streptomycin to the vestibular apparatus but probably more so to the acoustic apparatus. A number of cases of deafness have occurred following its use (Shane and Laurie, 1950 ; van Goidsenhoven and Stevens, 1950 , Bernard, Paley and Arnaud, 1950) Therapeutically, it is thought to be less effective than streptomycin weight for weight (Veterans Administration, 1950) Tubercle bacilli resistant to streptomycin are also resistant to dihydrostreptomycin Sometimes patients who repeatedly develop severe skin rashes or pyrexia with streptomycin will tolerate dihydrostreptomycin This would now seem to be the main indication for its use, but, as pointed out before, cases showing repeated reactions to streptomycin can usually be desensitized without difficulty.

PARA-AMINOSALICYLIC ACID

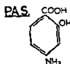
History

Para-aminosalicylic acid (P A S) was first described as a chemotherapeutic agent by Lehmann (1946) in Sweden Starting from the finding that salicylates stimulated the respiration of pathogenic tubercle bacilli he set out to see whether some substance differing only slightly from salicylic acid might block an essential bacterial metabolic process and thus have a bacteriostatic effect P.A S. was found to be much the most effective and also appeared to be active against experimental tuberculosis. The early results in man were suggestive (Lehmann,

1946) and further experience has confirmed that P A S. has a definite value in pulmonary tuberculosis (Medical Research Council, 1950a , Vallentin and his colleagues, 1950 , Swedish National Association against Tuberculosis, 1950) ; but it is probably a less powerful drug than streptomycin and its most important use at the present time is to suppress the emergence of streptomycin resistant tubercle bacilli.

Pharmacology

Para-aminosalicylic acid has the following structural formula



It is now usually supplied as the sodium or calcium salt, which are more stable and cause less gastro-intestinal upsets than the acid Hereafter the term " P A S " will be used to indicate the sodium or calcium salt of *para*-aminosalicylic acid The salt is usually a white crystalline powder, though some patches may be darker in colour without loss of potency P A S is usually taken by the mouth It is readily soluble in water, the colour of the solution varying from yellow to brown with different batches and tending to darken on standing The salt is more stable than the acid and in solution will not deteriorate up to 2 weeks When kept for long periods there is a danger of loss of potency so that a mixture when made up should be consumed within a fortnight The solution has an unpleasant taste, similar to that of other salicylates Various flavouring agents have been used but the taste is difficult to disguise and most patients prefer a 20 per cent solution in tap water As an alternative rice-paper cachets containing 1 5 or 2 grammes are available. The cachet is dipped in water and can then usually be swallowed without difficulty

Dosage

The dose recommended for adults is 5 grammes of the salt four times a day This dose has been shown to be effective in decreasing the incidence of streptomycin-resistant tubercle bacilli in patients receiving streptomycin in doses of 1 gramme a day (Medical Research Council, 1950a) It is probable that doses of less than 20 grammes of P A S a day are less effective, though it is possible that doses of 12–15 grammes a day may be adequate when 1 gramme of streptomycin is given only twice a week P A S can be administered intrapleurally in 20 per cent, 20 millilitres being given 2–3 times a week The solution must be sterilized by filtration, not by autoclaving Intramuscular injection is painful and is not recommended If estimates of pleural concentration are being made procaine should not be used as the local anaesthetic because the aminobenzene group will give a reaction similar to P A S , a local anaesthetic not containing this group, such as Xylocaine, should be substituted

Absorption

P A S is rapidly and totally absorbed from the intestine (Way and his co-workers, 1948) Blood serum levels vary from case to case and in the same case from time to time In patients on 5 grammes of P.A S by the mouth four times a day, serum levels varying from 3 to 13 milligrams per 100 millilitres are usually obtained at 1 hour after a dose and from 1 to 7 milligrams per 100 millilitres

at 4 hours. Twelve hours after the evening dose the level is usually under 1 milligram per 100 millilitres and sometimes no P.A S. can be detected.

Distribution

At plasma levels between 4 and 10 milligrams per 100 millilitres, 50–60 per cent of the P.A S. is bound to protein In the body the drug is widely distributed, the highest concentrations occurring in the lungs, liver and kidneys When given by the mouth in 3-gramme doses 6-hourly, levels of 0·5–4 milligrams per 100 millilitres have been obtained in pleural effusions 2 hours after the last dose (Lawrence and Comden, 1950) , on 5 gramme doses 4 times a day I have found similar ranges, with a peak 3 hours after the dose and detectable levels still present 12 hours after the evening dose. After intrapleural injection of 3 grammes of P A S. levels of 80–100 milligrams per 100 millilitres have been found in the pleural fluid at 6 hours, 20–30 milligrams per 100 millilitres at 24 hours, and 0–1 milligrams at 36 hours P A.S was detectable in the blood 1 hour after the intrapleural injection (Lawrence and Comden, 1950). On a daily dose of 12–14 grammes levels of 1–5 milligrams per 100 millilitres have been found in the sputum (Erdei, 1948).

Excretion

P.A S is rapidly excreted by the kidneys About 85 per cent of the dose can be accounted for in the urine within 10 hours About three-quarters of the P A.S. is excreted by the kidney tubules and the remainder is filtered by the glomeruli , it is possible that some of the latter is re-absorbed by the tubules (Horne and Wilson, 1949) The tubular excretion can be decreased by caronamide (Horne and Wilson, 1949), but the large doses of the latter necessary (4 gramme, 4-hourly) make its use impracticable. Benamid, which has a similar effect but is given in smaller doses, is at present under investigation as a substitute for caronamide (Boger and his associates, 1950), but cannot yet be recommended The urine of patients receiving P A S may reduce Benedict's reagent and so simulate glycosuria

Antagonists

The action of P A S. is antagonized by *para*-aminobenzoic acid

Mode of action

P A S. is bacteriostatic but not bactericidal The precise way in which it damages the tubercle bacilli is unknown

Toxicity

Gastro-intestinal upsets

Gastro-intestinal upsets occur in about 50 per cent of patients treated with P A S. Nausea and anorexia are common and, if severe, may lead to vomiting These symptoms can often be avoided by giving the drug towards the end of a meal or by using the rice-paper cachets mentioned above. If such devices are unsuccessful it is worth reducing the dose to 10 grammes a day, which is usually well tolerated, and then increasing slowly to the full dose But in severe cases the P.A S may have to be stopped Diarrhoea may be troublesome , if necessary

it can be treated with small doses of tincture of opium. Here also relief can sometimes be obtained by lowering the dose of P.A S temporarily and then slowly increasing

Rashes and fever

Rashes may occur, usually in the first week or two of treatment The rash is commonly erythematous, sometimes urticarial ' When mild the rash will frequently clear up without stopping the P A S though antihistamine drugs may be tried. Sometimes the rash may be severe and be accompanied by fever, even fatal cases of exfoliative dermatitis have occurred The drug will then have

Effect on kidneys

Serious nephrotoxic effects do not occur, but occasionally during treatment there may be a mild albuminuria, sometimes with an increase in red cells on microscopy Both will clear up as soon as the drug is stopped

Blood clotting time

On large doses of P A S a prolongation of the clotting time occurs within a few days, but it is not cumulative (Madigan and his colleagues, 1950). It is of no clinical significance unless there is liver disease or unless surgery is contemplated Under these circumstances 10 milligrams of synthetic vitamin K may be given daily by the mouth, this neutralizes the toxic effect.

Antipyretic action

P A S *is said to have a direct antipyretic action* (Madigan and his colleagues, 1950) This is thought to be due to the increased radiation of heat from the skin, which is in turn caused by peripheral vasodilatation

P.A.S. resistance

In a proportion of cases treated with P A S drug-resistant tubercle bacilli may be isolated, sometimes as early as the sixth week (Eastlake and Barach, 1949, Delaude and his associates, 1949, Carstensen, 1950) The method of testing for resistance, which is similar to that used for streptomycin resistance, is not yet entirely satisfactory and the clinical significance of resistance strains is not at present established, though they are more commonly found in cases with gross cavitation (Medical Research Council, 1950a) Nevertheless it seems wise, until more is known, to assume that patients with P A S-resistant bacilli are less likely to respond to the drug and that if these patients are treated with streptomycin the organisms may become resistant both to P A S and to streptomycin The incidence of P A S-resistant tubercle bacilli, according to the limited information at present available, seems much reduced by giving streptomycin at the same time (Medical Research Council, 1950a)

CLINICAL APPLICATION OF STREPTOMYCIN AND P A S

Streptomycin and P A S are the only drugs whose value in tuberculosis has been well established and their clinical use will be considered together As has

been already explained the action of both streptomycin and P.A.S in preventing the emergence of tubercle bacilli resistant to each other implies that in general they should always be used together. Unless otherwise stated the dose recommended will be 5 grammes of sodium or calcium *para*-aminosalicylate four times daily by the mouth and streptomycin 1 gramme daily in a single intramuscular injection

Primary tuberculosis

Chemotherapy is in general ineffective in primary tuberculosis in the lungs (Lorber, 1950) This is certainly true of the glandular component, though there is some evidence that streptomycin may be of value in the so-called "progressive primary" lesion (McEnery, Sweany and Turner, 1949)

Miliary tuberculosis

Recovery can now be expected in more than 50 per cent of cases of miliary tuberculosis treated with streptomycin (Medical Research Council, 1950b; Bunn, 1950, Bernard, Kreis, and their colleagues, 1949) The development of tuberculous meningitis is the main danger to life and this must be watched for by regular examination of the cerebrospinal fluid The appearance of miliary tubercles in the retina is a danger signal, as infection of the meninges is much commoner in such cases Meningitis may develop during the course of treatment or in a relapse If it does occur intrathecal streptomycin must be given

The initial dose of streptomycin should be 1 gramme twice a day, which may be reduced to 1 gramme a day when the temperature falls For children the dose should be 0 02 gramme per pound body-weight per day. Although streptomycin-resistant tubercle bacilli are seldom isolated it is wise to use P.A S. as well as streptomycin, both as a precaution against the risk of resistance and for its synergistic effect Treatment should be continued for at least 6 months, in severe cases for longer After stopping treatment the patient must be very carefully watched for 2 years or more as relapses are common On the whole the longer the course of treatment the less likely is a relapse to occur. A relapse may respond to a second course of treatment but it is rather less likely to do so.

Pulmonary tuberculosis

In pulmonary tuberculosis (Medical Research Council, 1948, 1950; Veterans Administration, 1950) the best response to chemotherapy is obtained in recent exudative disease, especially when the shadows in the radiograph are not confluent Such lesions are particularly likely to be seen when a patient already under observation is found to have had a recent spread of disease The response in cases of this kind is usually gratifying On the other hand chronic fibrocaseous disease is seldom affected and it is useless to try to close old thick-walled cavities by any but mechanical means In such cases chemotherapy should only be used, if at all, in order to clear up any more susceptible lesions which may be held up by the institution of collapse therapy Indeed as a rule one should

chemotherapy has been stopped. Tension cavities will occasionally close dramatically, probably owing to the effect of streptomycin in tuberculous disease in the draining bronchus, but it is wise to consolidate any gain by following up with collapse therapy In most cases of tuberculous broncho-pneumonia collapse therapy is not feasible in the acute stages and in many will never become so on rest in bed alone In such cases the prognosis is bad and it is proper to treat them in the first instance with streptomycin and P A S, primarily with the idea of rendering them fit for collapse therapy later There is no doubt that chemotherapy has greatly improved the outlook in this type of disease (Medical Research Council, 1948a, 1950a), and occasionally the result is so satisfactory that no collapse measures are necessary When the pneumonic lesions are more confluent, approaching a condition of tuberculous lobar pneumonia, the response is in general less satisfactory (Kirby, Simpson and Creger, 1949), though there is often initial improvement (Allison, 1947), extensive cavitation is liable to occur in the consolidated area and collapse measures may be technically difficult In addition, when streptomycin was used alone, the tubercle bacilli were liable to become highly streptomycin-resistant It is possible that cases of this kind will do better under combined therapy with streptomycin and P A S

Palliative use of chemotherapy

It must be very strongly emphasized that chemotherapy should never be used as a palliative or temporizing measure in pulmonary tuberculosis The only exceptions to this rule are when tuberculous laryngitis, enteritis or mouth ulcers are causing severe symptoms in advanced and hopeless cases In these circumstances it may be justifiable to use streptomycin and P A S in short courses in order to obtain symptomatic relief

Chemotherapy as part of a programme

In general chemotherapy should only be used as part of a programme aimed at securing arrest or cure of the disease It is highly dangerous to finish a course and leave the patient with an unclosed cavity, relapse is all too likely The aim should be to institute collapse during, or immediately after, the course Formerly it was often considered that there should be a standard length of course As resistant tubercle bacilli usually emerged within the first 2 or 3 months and it was found that the greatest improvement occurred during this period, treatment was not prolonged for more than 4 months Now that it is known that P A S greatly reduces the incidence of streptomycin-resistant bacilli there is less logic in this attitude, and it would seem proper to have a definite aim in each individual case This aim is usually to make the patient fit for collapse therapy and treatment should be continued until the aim is achieved or the result is despaired of Sometimes this will be only a matter of a few weeks When the desired result has not been obtained in 3 or 4 months it is possible, but not yet definitely known, that there is some increased risk of the emergence of resistant tubercle bacilli, but it is just in these cases, [illegible]
the risk is most worth taking [illegible]
for 6 or 8 months in the ho[illegible]
measures on which the patient's life depends

How long chemotherapy should be continued after the initiation of collapse therapy is uncertain and it is difficult to generalize. Some clinicians will induce an artificial pneumothorax or advise thoracoplasty in cases under chemotherapy at a more acute stage of the disease than would have been their custom before streptomycin was available In such cases it is reasonable to continue chemotherapy for a period. Tuberculous pneumonia, especially when it is basal and cavitating, is often treated with phrenic crush and pneumoperitoneum at an early stage; in spite of this early collapse it is worth while giving a prolonged course of chemotherapy, as the prognosis in these cases is so bad.

Minimal lesions

While there was such a big risk of the emergence of streptomycin-resistant tubercle bacilli it was certainly unjustifiable to give streptomycin to cases with minimal lesions The success of the combined treatment with P.A.S. and streptomycin reopens the subject, but it has not yet been shown in these cases either that this treatment is effective or that it is without risk. The toxic effects of the drugs, accepted as a proper hazard in severe disease threatening life, will bulk much larger when considering the treatment of a patient who may be relatively free from symptoms. It must also be remembered that the risk of streptomycin-resistant bacilli emerging has been diminished but not abolished Until more is known it can only be recommended that such cases should not be treated with chemotherapy

The unstable case

Certain cases, usually with somewhat disseminated nodular lesions, may pursue an irregular course of alternating improvement and deterioration It was hoped that streptomycin might encourage a permanently favourable trend (Howlett and O'Connor, 1948), but it has been found that the improvement has usually proved only temporary This was the conclusion of trials using streptomycin alone It is possible that more prolonged treatment with both streptomycin and P.A.S might be more effective

Tuberculous bronchitis

Involvement of the smaller bronchi, for instance those draining cavities, is very common, if not the rule, in pulmonary tuberculosis, but the term " tuberculous bronchitis " or "tracheo-bronchial tuberculosis" is usually reserved for conditions in which the mucous membrane of one of the larger bronchi is affected by tuberculous ulceration or granulation tissue Such lesions will therefore usually be visible through the bronchoscope

Tuberculous bronchitis responds well to streptomycin and P A S if the lesion is relatively recent and the parenchymal lesion slight or well controlled (Brewer and Bogen, 1947, Davis, 1949; Medical Research Council, 1951). It is best to follow the progress by repeated bronchoscopy at monthly or 2-monthly intervals and to continue treatment for at least a month after the lesion has apparently healed Not uncommonly the bronchoscopy after 6 or 8 weeks treatment will show that though continuity has been restored the mucous membrane has become grossly swollen and oedematous, perhaps with even greater narrowing

of the lumen than before treatment began With further therapy this oedema usually disappears In the most successful cases the bronchial appearances return to normal, but it is common for the lesion to heal leaving a greater or lesser degree of bronchial stenosis due to a fibrous stricture The future course of the case will depend on the degree of this stricture, its site and the lesions that are present beyond it If the stricture occurs in an upper lobe bronchus, unless the bronchus is almost completely occluded the drainage is usually adequate and secondary infection is uncommon , but if a lower lobe bronchus is affected, even if the patient's sputum is permanently converted, repeated secondary infections are liable to occur beyond the stricture The result is recurrent respiratory illnesses, often leading to bronchiectasis, even if this is not already present as a legacy of the original tuberculosis In cases of this kind it may be necessary to recommend lobectomy, in spite of the apparent healing of the tuberculous lesion In other cases, though the visible bronchial lesion heals, the sputum may remain positive owing to peripheral tuberculous bronchiectasis , here again resection may be advisable

When the presence of tuberculous bronchitis is holding up the institution of collapse therapy for a parenchymal lesion, it is wise to start the collapse as soon as bronchoscopy indicates that the bronchitis is reasonably well under control This will assist the healing of both lesions

In primary tuberculosis bronchial stenosis or occlusion may occur as the result of pressure by an affected gland or of actual rupture of the gland into the bronchial lumen There is no present evidence that chemotherapy is of any benefit in such cases

Tuberculous laryngitis

This lesion (Black and Bogen, 1947 , Bernard, Lotte and Arnaud, 1949) is dealt with elsewhere (*see* page 443) In general if the lung lesion is under control cases of tuberculous laryngitis respond well to chemotherapy Pain is rapidly relieved, though objective improvement takes a good deal longer The lesion may heal with marked fibrous stricture which poses mechanical problems In advanced and hopeless cases of pulmonary tuberculosis complicated by tuberculous laryngitis it may be justifiable to give short courses of chemotherapy for a week or two at a time in order to relieve pain

Primary pleural effusions

There is at present little information about the chemotherapy of primary pleural effusions While the emergence of drug-resistant tubercle bacilli remained a serious problem, the use of streptomycin was certainly unjustifiable in these cases Though the risk is now much less, chemotherapy has not yet been shown to be of value and should not at present be recommended It must be remembered that primary pleural effusions run a very variable course Only a carefully controlled trial could show whether the treatment was of any real value , the most important benefit to be looked for would be a reduction in the number of cases in which overt pulmonary tuberculosis later develops Nevertheless in the very exceptional patients whose condition gives serious cause for anxiety in the acute stage, it is probably justifiable to give at least a short course of streptomycin and P A S Dramatic improvement may be seen in such cases.

Tuberculous empyema

Very variable results have been reported in the treatment of tuberculous empyema with streptomycin (Hinshaw, Feldman and *Pfuetze, 1946; Bernard*, Lotte and Laumonier, 1949, Christensen, 1950) Failure to respond has been attributed to the acid reaction of tuberculous pus, the large number of bacilli which may be present, failure of the drug to penetrate the thickened pleura, or to a combination of these factors, but it must be remembered that the fate of a tuberculous empyema is bound up with the fate of the lesion in the underlying

unsuccessful artificial

mechanical reasons,

continue to exert its malign influence on the pleural condition. It is clear that control of the cavity will be the primary consideration and the chemotherapy can at best play only a subsidiary part It is possible that factors of this kind may account for the variable results reported

As mentioned above streptomycin is less effective in an acid medium The reaction of tuberculous pus is often between pH 6 and pH 7 and good results have been claimed for combining intrapleural and intramuscular streptomycin with an attempt to alkalinize the pleural contents (Christensen, 1950) For this *purpose 200–300 millilitres of 1 5 per cent sodium bicarbonate may be run into* the pleural cavity every second or third day, after aspiration of the pus, the quantity of alkali being decreased as the amount of pleural fluid diminishes It has been shown that this does alter the pH of the fluid towards the alkaline side. Streptomycin in the usual doses is given intramuscularly and 0 5 or 1 gramme is given intrapleurally every second or third day Intrapleural doses as high as 3 grammes have been given every third day without adverse effect, but if these large doses are given intramuscular therapy should be omitted to avoid toxicity; there is usually excellent absorption into the blood stream from the pleura. One should certainly give oral P A S in addition to streptomycin.

Much has been claimed for P A S in tuberculous empyema (Gilliard, 1949) Twenty millilitres of a 20 per cent solution may be given intrapleurally once or twice a week. No carefully controlled trials have been carried out and on the whole experience in Great Britain has been disappointing

It seems unlikely that, in general, chemotherapy will replace other methods of treatment for tuberculous empyema, but when the acute onset of fluid under an artificial pneumothorax, accompanied by severe general symptoms, seems to *threaten an empyema, it is justifiable to employ chemotherapy and aspiration as*

of other measures, unless the response is clear-cut and maintained

The use of chemotherapy in chest surgery

Resection.—It is generally agreed that resection for pulmonary tuberculosis should always be carried out under a protective cover of chemotherapy (Moore and *his colleagues, 1949) Although there has been no carefully controlled trial*, most surgeons are convinced that their results have been much improved since the

introduction of streptomycin. When the object is merely to provide a cover for the operation the course may be started 3 days before the operation and continued for 6 weeks If, in addition, the aim is to reduce sputum before the operation or to clear up a lesion elsewhere in the lung, a longer pre-operative course will obviously be necessary If there is any doubt that a residual lesion may remain after resection it is wise to continue the chemotherapy for several months at least after the operation

Thoracoplasty.—The occurrence of post-operative spreads of disease after thoracoplasty is not sufficiently frequent to justify using chemotherapy as a routine cover for operation, nor is there good evidence that such a cover substantially reduces the incidence of spread , but when a spread has occurred it usually responds excellently to chemotherapy Of course in a number of patients chemotherapy will be necessary in order to obtain sufficient improvement to make thoracoplasty feasible at all In these cases it is well to operate while the patient is still receiving chemotherapy, or as soon as possible thereafter

Tuberculous infections of the extrapleural space

On the whole tuberculous infections of the extrapleural space respond well to streptomycin and P.A S The drugs should be given by the usual routes and in addition 1 gramme of streptomycin should be injected into the space when the pus is aspirated.

Tuberculous sinuses

Tuberculous sinuses (Brock, 1947 , Veterans Administration, 1948 , Davis, 1949) respond exceedingly well to chemotherapy even when they have been present for long periods Treatment should be continued for at least a month after the sinus has healed When the sinus originates in a pocket of pus or a bone sequestrum this will have to be dealt with at the same time

THE SULPHONES

History

In 1938 Rich and Follis (1938) showed that sulphanilamide had an inhibitory effect in experimental tuberculosis in the guinea-pig The following year Feldman and Hinshaw (1939, 1940) found that sulphapyridine had a similar action The original sulphone, diaminodiphenyl sulphone (D D S), was evolved by Buttle

of D D S have been evolved with the object of obtaining maximal efficacy with minimal toxicity

All the sulphones have very definite toxic effects in man when given for long periods Although many workers consider that both the toxic and the therapeutic effects of these substances depend on the degree to which they are broken down to the parent sulphone, D D S , it is claimed that 2 of the more recently introduced derivatives, Promizole and Sulphetrone, are tuberculostatic in their own right and are not broken down to D D S to any extent Bernard, Nouvion, and their colleagues (1950) have recently reported that D D S , given at the same time as

streptomycin, reduced the incidence of streptomycin-resistant tubercle bacilli by almost 50 per cent The patients had chronic cavitated disease and the clinical value of the treatment could not be assessed

Pharmacology

The following are the more important sulphones which have been used in clinical practice. Although several of them can be given intravenously it is thought that they are more effective when given by the mouth ·

Promin (sodium *p* : *p*′-diaminodiphenyl sulphone N,N′-didextrose sulphonate) (Pfuetze and Pyle, 1949) —It is recommended that in adults 0·4 gramme a day should be given in divided doses, increasing gradually, according to tolerance, to a maximum of 0 8 gramme a day A final dose of 1 2 to 1·6 grammes a day is preferable if it can be tolerated The drug should be continued for a minimum of 4 months and preferably up to a year

Diasone (disodium formaldehyde sulphoxylate diaminodiphenyl sulphone) — This sulphone is rather less liable to cause anaemia than is Promin but it is thought to be less effective therapeutically (Pfuetze and Pyle, 1949)

Promizole (2 . 4-diaminophenyl 5′-thiazolyl sulphone) —This substance is well tolerated in adults in doses of 10–15 grammes a day (Pfuetze and Pyle, 1949) In children it is given in 6-hourly doses, working up gradually from 1 gramme a day initially to a final dose of 2 grammes or more and aiming at a blood serum level of 1–3 milligrams per 100 millilitres

Sulphetrone (Tetrasodium 4 · 4′-bis (γ-phenyl-*n*-propylamino)-diphenyl sulphone α γ α′ γ′-tetrasulphonate (Brownlee, Green and Woodbine, 1948; Brownlee and Kennedy, 1948).—In adults a dose of 0·5 gramme 4-hourly is gradually increased until the patient is taking 9 grammes a day. The aim is to achieve a blood serum level of 5–8 milligrams per-100 millilitres

D D S. (*p* · *p*′-diaminodiphenyl sulphone)—has been given (Bernard, Nouvion, and their colleagues, [illegible] a day, increasing at weekly intervals fo [illegible] y. This dose was contin [illegible] lly in the early stages

Antagonists

The action of sulphones is inhibited by *para*-aminobenzoic acid and by local anaesthetics, such as procaine, containing an amino group attached to a benzene ring

Toxicity

Promizole appears to have a relatively low toxicity, but toxic effects are very definite with the other drugs The patients often become blue in colour and methaemoglobin is present in some cases Headache, nausea and vomiting are frequent. Rashes may occur and thyroid enlargement is common The patients usually become anaemic, and this is due to three different factors An unabsorbable compound is formed with the alimentary iron , this can be counteracted by giving iron by the mouth Secondly, the sulphones are thought to prevent the manufacture of a metabolite essential to blood formation by their effect on the

intestinal flora; this effect can be overcome by giving yeast Finally, there is a haemolytic effect of the drug and no method has yet been found of correcting this

Results

The evidence for the effect of the sulphones in pulmonary tuberculosis is anecdotal and not very convincing Pfuetze and Pyle (1949) thought Promin was of definite value but that the effect of diasone was doubtful Burns and his colleagues (1949) were unable to demonstrate any effect of Promizole in a trial with matched controls in tuberculous cases in a mental hospital On the other hand, Lincoln and Kirmse (1949) treated miliary tuberculosis with Promizole alone and 5 out of 7 children treated for more than a month survived for over 4 years. With Sulphetrone possible favourable effects in pulmonary tuberculosis have been reported (Anderson and Strachan, 1948, Clay and Clay, 1948), but Morlock and Livingstone (1949) concluded that it was of little value There is evidence that diaminodiphenyl sulphone (D D S) has a suppressive effect on the emergence of streptomycin-resistant tubercle bacilli (Bernard, Nouvion, and their colleagues, 1950), but this effect appears to be considerably less than that of P A S There are as yet no adequate data about its direct clinical value

Conclusion

Although the sulphones have a definite suppressive effect in the tuberculosis of animals there is no clear-cut evidence of their clinical value in man In addition, with the possible exception of Promizole, their toxic effects are far from negligible D D S, at least, has a definite suppressive effect on the emergence of streptomycin-resistant tubercle bacilli, though this effect seems less than that of P A S The sulphones can, therefore, only be recommended at present in cases in which tubercle bacilli are resistant to streptomycin and P A S or who for some reason are completely intolerant to these drugs

THE THIOSEMICARBAZONES

History

The thiosemicarbazones were first described as tuberculostatic agents by Domagk (1946) In investigating the effect of the sulphonamides on tubercle bacilli he had found that sulphathiazole and sulphathiodiazole were much the most effective It seemed possible that the increased effect was conferred by the thiazole group and this led him to try the thiosemicarbazones from which sulphathiodiazole was manufactured Since Domagk's original description the thiosemicarbazone drugs have been widely used in Germany and to a lesser extent elsewhere

Pharmacology

The thiosemicarbazone (Behnisch, Mietzsch and Schmidt, 1950) which has been mainly used clinically is 4-acetyl-amidobenzaldehyde thiosemicarbazone ($CH_3CONH\langle\rangle CH{=}N\ NH\ CS\ NH_2$) *Thiacetazone may be adopted as the* official name in Great Britain It was originally labelled TB1/698 by Domagk and has been called commercially Conteben in Germany, Thioparamizone in Great Britain and Myvizone or Tibione in the United States It is a pale yellow, slightly crystalline substance, almost insoluble in water and only slightly

soluble in organic solvents with the exception of propylene glycol. The solubility in water may be increased by dissolving the drug in a solution of antipyrine; but thiacetazone is usually given by the mouth

Resistance

Although little work has been done on this aspect, several cases have been reported in which tubercle bacilli resistant to thiacetazone have been isolated from patients under treatment (Davis and Schwartz, 1950; Auersbach and Schutz, 1950) At the time of writing it is not known whether combined treatment with thiacetazone and streptomycin or P A S. will prevent the emergence of bacilli resistant to either of these drugs

Mode of action

The thiosemicarbazones are bacteriostatic rather than bactericidal. The precise mode of action is unknown, but the effect is not antagonized by *para*-aminobenzoic acid or cysteine.

Dosage

There is no firm agreement as to the optimal dosage (Mertens and Bunge, 1950, Hinshaw and McDermott, 1950) Individuals vary in their tolerance of the drug The patient should start on a daily dose of 12 5–25 milligrams which may be given in divided doses 1–4 times a day After 1–2 weeks the dose is gradually increased to a maximum of 150 milligrams a day It is probably safer not to exceed 100 milligrams a day though some workers consider that therapeutic effects are only obtained in doses bordering on the toxic. Treatment has been continued for a year or more in individual cases Intrapleurally 0·1–0·5 gramme has been given suspended in physiological saline solution 1–3 times a week

Toxicity

Nausea, anorexia and sometimes vomiting are common, especially early in treatment and with larger doses Jaundice and fatty infiltration of the liver have occurred in a substantial number of cases Although it has been contended that the liver damage is not due to the drug it is wise to assume for the present that hepatic injury is a risk and to carry out liver function tests before and at intervals during treatment. Most of the recorded cases of liver damage have recovered when the drug was stopped Agranulocytosis is uncommon but severe cases have occurred, so leucocyte counts must be done regularly. Haemolytic anaemia has been noted in patients on doses above those recommended here; a mild microcytic anaemia is common in those on lower doses. Rashes, usually erythematous but sometimes urticarial, are not uncommon and conjunctivitis may occur (Hinshaw and McDermott, 1950, Simmons and his colleagues, 1950)

Results

No well controlled clinical trials have been carried out with thiacetazone, so that its usefulness is difficult to assess (Mertens and Bunge, 1950; Hinshaw and McDermott, 1950). It is clear that it is unsuccessful in miliary and meningeal tuberculosis On the other hand, it is claimed that the results in tuberculous

laryngitis and tuberculous enteritis are comparable to those with streptomycin *In pulmonary tuberculosis it is said that, as with other drugs, cases with recent* exudative disease respond best If the blood sedimentation rate is raised, there is usually a dramatic fall within a few days, but this is regarded as a specific effect on the test rather than an indication of amelioration of the disease On the whole it seems likely that the results may be comparable to those obtained with P A S Success has been claimed in early trials of treatment with thiacetazone and P A S simultaneously (Brandner, 1950) There is no doubt that the results with thiacetazone alone are inferior to those with streptomycin

Conclusion

The value of the thiosemicarbazones cannot yet be regarded as established but it is clear that they are potentially toxic There can be little at present to recommend their use except in patients intolerant to streptomycin or P A S or whose organisms have become resistant to those drugs The thiosemicarbazones should only be used in hospital where a proper watch can be kept for the toxic effects

GENERAL CONCLUSIONS

During the current period of intensive research any conclusions about the use of chemotherapy are liable to become rapidly out of date Nevertheless at the present time it is clear that streptomycin and the salts of *para*-aminosalicylic acid are the drugs to be generally employed Owing to their relatively greater toxicity and lesser effectiveness the sulphones and the thiosemicarbazones will usually be reserved for patients whose tubercle bacilli have become resistant to streptomycin or P A S , or who have become intolerant of these drugs

As regards the indications for this form of treatment, cases of miliary tuberculosis must always of course be treated with chemotherapy Cases of severe acute pulmonary tuberculosis should have streptomycin and P A S in the first instance, usually in order to prepare them for collapse therapy Cases of tuberculous bronchitis should also have chemotherapy, though control of the parenchymal lesion is equally important Chronic fibrocaseous lesions are unlikely to respond and should be treated by other means In the less acute pulmonary lesions, in minimal lesions, in pleural effusions and in tuberculous empyemas the value and risks of the combined treatment with streptomycin and P A S are not certainly known One thing is clear , however successful the initial reaction to treatment no patient must be left with an unclosed cavity, to do so is to invite disaster and to render futile the risks and discomfort that chemotherapy entails

ANALOGUES OF NICOTINAMIDE

As we go to press three new drugs have been reported which are claimed to be effective against tuberculosis They are analogues of nicotinamide The most active *is said to be iso-nicotinic acid hydrazide and the other two are its glucosyl* derivative and 1-*iso*-nicotinyl-2-isopropyl hydrazide They were first described by Meyer and Mally (1912) and subsequently rediscovered by Fox (1951)

The drugs are rapidly absorbed from the intestine *Iso*-nicotinic acid hydrazide has been given orally two or three times a day in doses of 50-100 milligrams

Few toxic side effects have so far been encountered, but constipation, difficulty in initiating micturition, tremor, exaggeration of the deep reflexes and extensor plantar responses have been reported in individual patients. Special caution is advisable in patients with renal disease. Preliminary reports from experienced investigators, and limited personal experience, suggest that *iso*-nicotinic acid hydrazide has the same range of effectiveness as streptomycin and P.A.S. in combination. Nothing is yet known about the emergence of drug resistance (Robitzek and Selikoff, 1952). The precise place of this group of drugs is at present being determined by controlled investigations.

BIBLIOGRAPHY

Allison, S T. (1947) "Streptomycin in Tuberculous Pneumonia." *Amer Rev Tuberc*, 56, 401

Anderson, T, and Strachan, S J (1948) "Chemotherapy of Pulmonary Tuberculosis with Sulphetrone" *Lancet*, 2, 135

Auersbach, K, and Schutz, I (1950) "Resistance to TB I" *Klin Wschr*, 28, 373

Beham, H, and Perr, H (1948) "Stomatitis due to Streptomycin, report of 3 cases" *J Amer med Ass*, 138, 495

Behnisch, R, Mietsch, F, and Schmidt, H (1950) "Chemical Studies on Thiosemicarbazones with particular reference to Anti-tuberculous Activity" *Amer Rev Tuberc*, 61, 1

Bernard, E., Kreis, B, Lotte, A, Paley, P Y, and Mantoux, G (1949) "Miliary Tuberculosis and its Treatment with Streptomycin" *Sem Hop, Paris* 25, 2087

— Lotte, A, and Arnaud, G (1949) "Treatment of Tuberculous Larynx and Pharynx with Streptomycin" *Ibid*, 25, 2111

— — and Laumonier, M (1949) "Treatment of Tuberculous Pyopneumothorax with Streptomycin" *Ibid*, 25, 2109

— Nouvion, Coletsos, P J, and Kreis, B (1950) "Lessening the Risk of Streptomycin Resistance in Combined Sulphone-streptomycin Treatment A study of 300 cases of Pulmonary Tuberculosis" *Bull Acad nat Med, Paris*, 134, 461

— Paley, P Y, and Arnaud, G (1950) "Sur l action toxique cochléo-vestibuleine de la dihydrostreptomycine" *Bull Soc med Hop, Paris*, 66, 583

Bignall, J R, and Crofton, J W (1949) "Antihistamine Drugs in Treatment of Nausea and Vomiting due to Streptomycin" *Brit med J*, 1, 13

— — and Thomas, J A B (1951) "Effect of Streptomycin on Vestibular Function." *Brit med J*, 1, 554

Black, M, and Bogen, E (1947) "Streptomycin in Tuberculous Laryngitis" *Amer Rev Tuberc*, 56, 405

Boger, W P, Beatty, J O, Pitts, F W, and Flippin, H F (1950) "The Influence of a New Benzoic Acid Derivative on the Metabolism of Para-aminosalicylic Acid (PAS) and Penicillin" *Ann intern Med*, 33, 18.

Brandner, R (1950) "Combined P A S -T B I Therapy of Tuberculosis" *Dtsch med Wschr*, 75, 1295

Brennan, A J, and Wichelhausen, R H (1949) "Streptomycin Resistant Tubercle Bacilli Isolation of Resistant Organisms from Pleural Fluid Prior to institution of Streptomycin Therapy" *J Amer med Ass*, 140, 1275

Brewer, L A, and Bogen, E (1947) "Streptomycin in Tuberculous Tracheo-bronchitis" *Amer Rev Tuberc*, 56, 408

Brownlee, G, Green, A F, and Woodbine, M (1948) "Sulphetrone, a Chemotherapeutic agent for tuberculosis Pharmacology and chemotherapy" *Brit J Pharmacol*, 3, 15

— and Kennedy, C R (1948) "The Treatment of Experimental Tuberculosis with Sulphetrone" *Ibid*, 3, 29

— — "The Chemotherapeutic Action of Streptomycin, Sulphetrone and Promin in Experimental Tuberculosis" *Ibid*, 3, 37

Brock, B L (1947) "Streptomycin in the Treatment of Draining Tuberculous Sinuses" *J Amer med Ass*, 135, 147

Bunn, P A. (1950) "Two-year follow up report of Patients with Miliary and Meningeal Tuberculosis Treated with Streptomycin" *Amer J med Sci*, 219, 127

Burns, H A, Feldman, W H, Hinshaw, H C, Myers, J A, and Pfuetze, K H (1949) "Treatment of Tuberculosis with Promizole A Clinical Investigation with Matched Controls" *Dis Chest.*, 16, 867

Carr, D T, Hinshaw, H C, Pfuetze, K. H, and Brown, H A (1949) "The Use of Dihydrostreptomycin in the Treatment of Tuberculosis" *Dis Chest*, 16, 801

Carstensen, B (1950) "Para-aminosalicylic Acid (PAS) in Pulmonary and Extra-pulmonary Tuberculosis" *Amer. Rev Tuberc.*, 61, 613

Christensen, O (1950). "Streptomycin Therapy in Tuberculous Empyema" *Acta tuberc Scand* Suppl, 26, p 62
Clay, M G, and Clay, A C (1948). "Chemotherapy of Tuberculosis with Sulphetrone" *Lancet*, 2, 180
Cohen, A C, and Glinsky, G C (1949). "Cutaneous Lesions Occurring in the Course of Streptomycin Therapy" *Arch Dermat Syph*, 60, 373
Corper, H J, and Cohn, M. L. (1949) "The Probable Mechanism of Streptomycin Action in Tuberculosis" *Yale J Biol Med*, 21, 181
Crofton, J (1950) "Discussion on Present Position of the Newer Antibiotics" *Proc. R Soc Med.*, 43, 692.
— and Foreman, H. M (1948) "Streptomycin Dermatitis in Nurses" *Brit med J*, 2, 71
Davis, R H (1949) "Streptomycin in Treatment of Tuberculous Sinuses Review of 11 cases" *Lancet*, 2, 982
Davis, J D, Schwartz, J A, and Pattison, E H. (1950) "Preliminary Observations of 25 Patients receiving Tibione" *Transactions of the 9th Streptomycin Conference*, p 96 Washington, Veterans Administration
Delaude, A, Karlson, A G, Carr, D T, Feldman, W. H, and Pfuetze, K H (1949) "Increase ... ervations on cultures
Don ... ber eine neue gegen ... aften, 33, 315.
Eastlake, C, and Barach, A L. (1949) "Use of P A S in Chronic Pulmonary Tuberculosis" *Dis Chest*, 16, 1
Erdei, A (1948) "*p*-Aminosalicylic Acid in Tuberculosis." *Lancet*, 2, 118
Feldman, W H, and Hinshaw, H C (1939) "Effect of Sulphapyridine on Experimental Tuberculosis in the Guinea-pig" *Proc Mayo Clin*, 14, 174
— — (1940) "Sulphapyridine in Experimental Tuberculosis" *Amer Rev. Tuberc*, 41, 732
— (1944) "Effects of Streptomycin on Experimental Tuberculosis in Guinea-pigs" *Proc Mayo Clin*, 19, 593
— — and Mann, F C (1945) "*Streptomycin in Experimental Tuberculosis*" *Amer. Rev Tuberc*, 52, 269
— — and Moses, H E (1940) "Effects of Promin on Experimental Tuberculosis" *Proc Mayo Clin*, 15, 695
Fitzgerald, G., and Hallpike, C. S (1942) "Studies in Human Vestibular Function Observations on the Directional Preponderance ('Nystagmus bereitscheft') of Caloric Nystagmus resulting from Cerebral Lesions" *Brain*, 65, 115
Iso-nicotine Acid Hydrazide
Fox, H H. (1951) "Synthetic Tuberculostats—Isonicotinic Aldehyde Thiosemicarbazone and some Related Compounds" 12th International Congress of Pure and Applied Chemistry, September, 9–13
Furtos, N C, and Doane, E A (1949). "Transmission of Streptomycin Resistant Tubercle bacilli in Man." *J Amer med Ass*, 140, 1274
Garrod, L P (1948) "The Bactericidal Action of Streptomycin" *Brit med J*, 1, 382
— (1950) "The Nature of the Action of Streptomycin on Tubercle bacilli" *Amer Rev Tuberc*, 62, 582
Gilliard, A (1949) "Statistical Notes on the Treatment of Tuberculous Empyema with PAS" *Schweiz med Wschr*, 79, 625
... (1950) "Severity and Significance of Acoustic Disorders ... med Wschr, 80, 1021.
... er, R. J. (1952) "On the Lasting ... Acid in the Experiment Tuberculosis
... tivity of Hydrazine Derivatives of ... n of Mice." *Quart Bull Seaview Hosp*, 13, 3.

Hinshaw, H C, and Feldman, W H (1945) "Streptomycin in Treatment of Clinical Tuberculosis" *Proc Mayo Clin*, **20**, 313
— — and Pfuetze, K H (1946) "Treatment of Tuberculosis with Streptomycin A Summary of Observations on 100 cases" *J Amer med Ass*, **132**, 778
— and McDermott, W (1950) "Thiosemicarbazone Therapy of Tuberculosis in Humans" *Amer Rev Tuberc*, **61**, 145
Hobson, L B, Tomsett, R, Muschenheim, C, and McDermott, W (1948) "Laboratory and Clinical Investigation of Dehydrostreptomycin" *Amer Rev Tuberc*, **58**, 501
Holt, H D, and Cruikshank, R (1949) "A simple Method of Determining the Streptomycin Sensitivity of Mycobacterium Tuberculosis" *Mon Bull Min Hlth*, **8**, 103
Horne, N W, and Wilson, W M (1949) "Effect of Caronamide on Excretion of p-Aminosalicylic Acid" *Lancet*, **2**, 507
Howlett, K S, and O'Connor, J B (1948) "Treatment of Tuberculosis with Streptomycin Response of sub-acute and chronic types" *Amer Rev Tuberc*, **58**, 139
Jensen, K A (1949) "Biological Studies on Streptomycin Therapy" *Acta tuberc scand*, Suppl **21**, p 42
Kirby, W M M, Simpson, R M, and Creger, W P (1949) "Streptomycin Therapy of Tuberculous Pneumonia in Negro Adults" *Amer Rev Tuberc*, **60**, 343
Lawrence, S H, Comden, N (1950) "Studies on the Behaviour of PAS in Tuberculous Pleural Effusions" *Dis Chest*, **18**, 430
Lincoln, N S, Horton, R, Stokes, A M, Monroe, J, and Riggins, H M (1950) "Dihydrostreptomycin in Pulmonary Tuberculosis" *Amer Rev Tuberc*, **62**, 572
Lincoln, E M, and Kirmse, T W (1949) "Streptomycin and Promizole in Miliary Tuberculosis and Tuberculous Meningitis in Children" *Lancet*, **1**, 767
Lehmann, J. (1946) "Para-aminosalicylic Acid in the Treatment of Tuberculosis" *Lancet*, **1**, 15
Lorber, J (1950) "Streptomycin and the primary Lung Lesion in Tuberculosis in Children" *Lancet*, **1**, 389
Madigan, D G, Griffiths, L L, Lynch, M J G, Bruce, R A, Kay, S, and Brownlee, G (1950) "Para-aminosalicylic Acid in Tuberculosis Clinical and Pharmalogical Aspects" *Lancet*, **1**, 239
McEnery, E T, Sweany, H C, and Turner, G C (1949) "Pulmonary Tuberculosis in Children Treated with Streptomycin" *Pediatrics*, **4**, 323
Medical Research Council (1948) "Streptomycin Treatment of Pulmonary Tuberculosis" *Brit med J*, **2**, 769
— (1948) "Streptomycin Treatment of Tuberculous Meningitis" *Lancet* **1**, 582
— (1948) "Specific Laboratory Tests in Streptomycin Therapy of Tuberculosis" *Ibid*, **2**, 862
— (1950) "Treatment of Pulmonary Tuberculosis with Streptomycin and Para-aminosalicylic Acid" *Brit med J*, **2**, 1073
— (1950) "Streptomycin in Acute Miliary Tuberculosis" *Lancet*, **1**, 841
— (1951) "Streptomycin Treatment of Tuberculous Lesions of the Trachea and Bronchi" *Lancet*, **1**, 253
Mertens, A, and Bunge, R (1950) "The Present Status of the Chemotherapy of Tuberculosis with Conteban, a substance of the thiosemicarbazone series A review" *Amer Rev Tuberc*, **61**, 20
Meyer, H, and Mally, J (1912) "Hydrazine Derivatives of Pyridine Carboxylic Acid" *Monatsch* 33, 400
Mitchison, D A (1950) "Development of Streptomycin Resistant Strains of Tubercle bacilli in Pulmonary Tuberculosis" *Thorax*, **5**, 144, 162
Moore, J A, Murphy, J D, and Elrod, P D (1949) "An Evaluation of Streptomycin as a Protective Agent in Pulmonary Resection for Tuberculosis" *J thorac Surg*, **18**, 45
Morlock, H V, and Livingstone, R (1949) "Sulphetrone in Pulmonary Tuberculosis" *Lancet*, **2**, 1170
National Research Council Committee on Chemotherapeutics (1946) "Streptomycin in the Treatment of Infections A Report of 1,000 cases" *J Amer med Ass*, **132**, 70

Pfuetze, K H , and Pyle, M. (1949). "Chemotherapy in Clinical Tuberculosis" *Proc Mayo Clin*, 24, 213
Pyle, M M (1947) "Relative Numbers of Resistant Tubercle Bacilli in Sputa of Patients [illegible]

Rev Tuberc, 65, 402.
— — (1952). "Tuberculous Chemotherapy with Hydrazine Derivatives of Isonicotinic Acid" *Dis Chest*, 21, 392
— — and Ornstein, G G (1952) "Chemotherapy of Human Tuberculosis with Hydrazine Derivatives of Isonicotinic Acid" *Quart Bull Seaview Hosp*, 13, 27
ment of Experimental Tuberculosis in Guinea-pigs" *Bull Johns Hopk Hosp.*, 62, 77.
Schatz, A , Bugie, E , and Waksman, S A. (1944) "Streptomycin, a Substance Exhibiting Antibiotic Activity Against Gram-positive and Gram-negative bacteria" *Proc. Soc exp. Biol, N Y*, 55, 66
Selikoff, I J , Robitzek, E H , and Ornstein, G G (1952) "Toxicity of Hydrazine Derivatives of Isonicotinic Acid in Chemotherapy of Human Tuberculosis" *Quart. Bull Seaview Hosp*, 13, 17
Shane, S J , and Laurie, J H (1950) "Neurotoxicity of Dihydrostreptomycin" *Canad med Ass J*, 63, 277.
Sievers, O (1949) "Sensitivity of Tubercle Bacillus." *Lancet*, 1, 798
Simmons, G , Hobson, L B , Resnick, A , De Nicola, R., and Bennett, R H (1950) "Human Pharmacology of *p*-formylacetanilide Thiosemicarbazone (Myvizone)" *Amer Rev. Tuberc.*, 62, 128
Smith, D G , and Waksman, S A (1947) "Tuberculostatic and Tuberculocidal Action of Streptomycin" *J Bact*, 54, 67
Steenken, W , D'Esopo, N D , and Wolinsky, E (1947) "Excretion of Streptomycin into Tuberculous Cavities Pleural Space and Tracheo-bronchial Tree" *Amer Rev. Tuberc*, 56, 403.
— and Pratt, P C (1949) "Streptomycin in Experimental Tuberculosis" *Amer. Rev Tuberc*, 59, 664
Sumner, J (1949) "A Clinical Report of three cases of Vitamin B Deficiency occurring during Streptomycin Therapy" *Tubercle, Lond*, 30, 62.
Swedish National Association against Tuberculosis, Therapeutic Trials Committee (1950) [illegible] Comparison between

of Pulmonary

f Tuberculous.
o April 1949."
Amer Rev Tuberc, 60, 715
Vallentin, G., Tornell, E., Beskow, A , Carstensen, B , Thune, R , Helleberg, G , and Lehmann, J. (1950) "P.A S in Pulmonary Tuberculosis" *Tubercle*, 31, 2
Veterans Administration (1948) "Streptomycin in the Treatment of Tuberculosis" *J Amer med Ass*, 138, 584
— (1950) "Current Status of the Chemotherapy of Tuberculosis in Man" *J Amer med Ass*, 142, 650
Watson, E H , and Stow, R M (1948) "Streptomycin Therapy. Effects on fetus" *J Amer med Ass*, 137, 1599
[illegible] (1948) "The Absorption,
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